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RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
44TH YEAR—ESTABLISHED 1956

SPECIAL ISSUE

INHALED NITRIC OXIDE
PART I

- The Biology of Nitric Oxide
- Use for Hypoxemic Respiratory Failure of the Newborn
- Pediatric Applications
- Use for the Acute Respiratory Distress Syndrome
- Use in Cardiac Disease
- Perioperative Use for Heart and Lung Transplantation
- Chronic Use for Pulmonary Hypertension

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Source: Barker SJ, Shah NK. The Effects of Motion on the Performance of Pulse Oximeters in Volunteers. *Anesthesiology* 1997;86(1):101-108.

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Source: Barker SJ, Novak S, Morgan S. The Performance of Three Pulse Oximeters During Low Perfusion in Volunteers. *Anesthesiology* 1997;87(3A):A409.

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CONTENTS

FEBRUARY 1999 / VOLUME 44 / NUMBER 2

SPECIAL ISSUE

JOURNAL CONFERENCE ON INHALED NITRIC OXIDE PART I

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CONFERENCE PROCEEDINGS

Foreword: Inhaled Nitric Oxide: The 1998 RESPIRATORY CARE Journal Conference
by Dean R Hess and William E Hurford—Boston, Massachusetts **155**

The Biology of Nitric Oxide
by Margaret Aranda—Philadelphia, Pennsylvania, and Ronald G Pearl—Stanford, California **156**

Inhaled Nitric Oxide for Hypoxemic Respiratory Failure of the Newborn
by Jesse D Roberts Jr—Boston, Massachusetts **169**

Pediatric Applications of Inhaled Nitric Oxide
by John Thompson, Scot T Bateman, and Peter Betit—Boston, Massachusetts **177**

Inhaled Nitric Oxide for Acute Respiratory Distress Syndrome
by Marlene Gerlach, Didier Keh, and Herwig Gerlach—Berlin, Germany **184**

Inhaled Nitric Oxide for Cardiac Disease
by George F Rich, Stuart M Lowson, and Victor C Baum—Charlottesville, Virginia **196**

Perioperative Use of Inhaled Nitric Oxide for Heart and Lung Transplantation
by Emile A Bacha—Boston, Massachusetts **205**

Long-Term Use of Inhaled Nitric Oxide for Pulmonary Hypertension
by Richard N Channick and Gordon L Yung—San Diego, California **212**

BOOKS, FILMS, TAPES, & SOFTWARE

Pulmonary Pathophysiology–The Essentials
reviewed by Christopher H Goss—Seattle, Washington **222**

UpToDate in Pulmonary Disease and Critical Care Medicine
reviewed by Noreen Roth Henig—Seattle, Washington **223**

The Survey Kit
reviewed by Derek Stanford—Seattle, Washington **224**

Self-Management of Asthma
reviewed by Kathy Boyle—Little Rock, Arkansas **225**

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ALSO IN THIS ISSUE

229 AARC Membership Application

136 Abstracts from Other Journals

240 Advertisers Index & Help Lines

240 Author Index

237 Calendar of Events

231 Call for OPEN FORUM Abstracts

233 Manuscript Preparation Guide

227 MedWatch

226 New Products & Services

238 Notices

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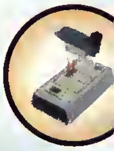

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Abstracts

Summaries of Pertinent Articles in Other Journals

Editorials, Commentaries, and Reviews To Note

Treating Patients with Severe Sepsis (review)—Wheeler AP, Bernard GR. N Engl J Med 1999;340(3):207-214.

Treatment of Asthma with Drugs Modifying the Leukotriene Pathway (review)—Drazen JM, Israel E, O'Byrne PM. N Engl J Med 1999;340(3):197-206.

Video-Assisted Thoracic Surgery—Rao A, Bansal A, Rangraj M, Grant GR, Papamichael MJ, Nepomuceno A, et al. Heart Lung 1999;28(1):15-19.

Complementary/Alternative Medicine for Asthma: We Do Not Know what We Need to Know—Ernst E. Chest 1999;115(1):1-3.

Steroids in COPD: The Nearly Eternal Question—Anthonisen NR. Chest 1999;115(1):3-4.

Antimicrobial Therapy of Ventilator-Associated Pneumonia: How to Select an Appropriate Drug Regimen—Kollef MH. Chest 1999;115(1):8-11.

Drug Administration by Jet Nebulization—Coates AL, Ho SL. Pediatr Pulmonol 1998;26(6): 412-423.

Mycobacterial Infection in Immunocompromised Patients—Washington L, Miller WT Jr. J Thorac Imaging 1998 ;13(4):271.

Mycobacterial infection, including both tuberculosis and nontuberculous mycobacterial infection, is an important cause of morbidity and mortality in immunocompromised patients, particularly those who are infected with the human immunodeficiency virus. When these patients have active tuberculosis, apical, often cavitary, opacities characteristic of postprimary tuberculosis remain among the more common radiographic presentations. However, unusual radiographic manifestations of tuberculosis are more common in immunocompromised patients than in the general population. Nontuberculous mycobacterial infection in immunocompromised patients is frequently hematogenously disseminated, and the appearance on chest radiography is varied. Among patients infected with the human immunodeficiency virus, unifocal or multifocal alveolar infiltrates and mediastinal lymphadenopathy are the most common manifestations.

Pulmonary Infections in Immunocompromised Patients Who Do Not Have Acquired Immunodeficiency Syndrome: A Systematic Approach—Conces DJ Jr. J Thorac Imaging 1998;13(4):234.

Immunocompromised patients are susceptible to infections by organisms that infect individuals with normal immunity and by organisms that affect only those with abnormalities in their immune system. Using the radiographic findings and incorporating clinical information allows for the creation of a useful list differential diagnoses. The nature of the immune defect must be defined because defects in the different parts of the immune system are associated with infections by specific organisms. The time interval since transplantation provides a diagnostic clue because infections tend to occur at certain time intervals after transplantation. An epidemiologic history provides a history of exposure to organisms that may produce pneumonia. Consideration of the therapy the patient has received provides additional clues to the cause of the pneumonia. The physical examination and laboratory studies may provide an indication of the cause of the infection. Organisms tend to produce infections that have a typical rate of clinical development. Classifying the presentation as acute, subacute, or chronic provides additional etiologic clues. Correlating the clinical information with the radiographic findings generates a list of the most likely causative organisms. The list is useful in deciding on additional diagnostic tests and guiding therapy.

Effects of Sputum Oscillations and rhDNase in Vitro: A Combined Approach To Treat Cystic Fibrosis Lung Disease—Dasgupta B, Brown NE, King M. Pediatr Pulmonol 1998; 26(4):250.

Mucolytic treatment with rhDNase is part of the current therapy for cystic fibrosis (CF) lung disease. The Flutter valve, a device for enhancing airway mucus clearance, has recently been approved for use in CF patients. Exhalation through the Flutter valve leads to oscillations of expiratory airflow, improving mucus viscoelasticity and stimulating clearance. The goal of our in vitro study was to evaluate the individual and combined effects of Flutter valve oscillations and rhDNase treatment on the viscoelastic (rheological) properties of CF sputum. Sputum specimens were collected from 19 CF patients and subjected to the following protocols: 1) baseline sample with no treatment applied; 2) application of oscillations generated by airflow through the Flutter valve; 3) incubation at 37 degrees C for 30 min with 10% vol/wt rhDNase (Pulmozyme) to achieve a final concentration of 2.5 microg/mL (approximately 100 nM); 4) combination of Flutter valve oscillations and 10% vol/wt normal saline (0.9% NaCl); 5) combination of Flutter valve oscillations and 10% vol/wt rhDNase at 2.5 microg/mL final concentration. For each protocol, the mucus rigidity index (log G* at 1 rad/s) was measured at baseline and at 30 min. Values are presented as mean±SEM. The cough clearability index

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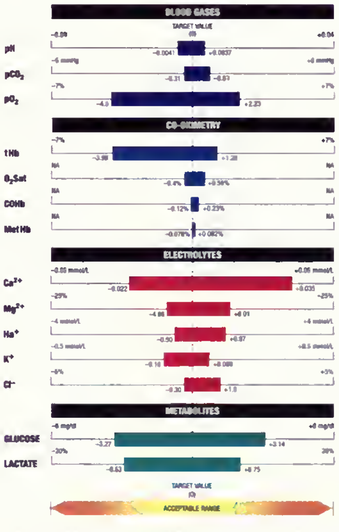

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(CCI) was computed from measurements of mucus viscoelasticity, based on relationships established in model studies. Flutter valve treatment alone did not result in a significant reduction in the rigidity of CF sputum (2.24±0.13 vs. 2.11±0.13, $p=0.19$), nor did rhDNase (2.5 microg/mL) alone, although we have previously shown (Pediatr. Pulmonol. 1995; 20:78) that both of these treatments reduce sputum spinnability, which is more sensitive to molecular weight reduction. In comparison to individual treatments, combined treatment with Flutter valve oscillations and rhDNase significantly reduced the mucus rigidity to 1.85±0.19 from 2.24±0.13 ($p< 0.001$), consequently increasing the predicted clearability of the sputum (from 1.09±0.26 to 1.83±0.48, $p=0.012$). These in vitro results suggest that a combination of biochemical treatment (e.g., DNase) and mechanical oscillation may have a better therapeutic potential for mucus clearance in CF lung disease.

Recurrent Cough: Natural History and Significance in Infancy and Early Childhood—Brooke AM, Lambert PC, Burton PR, Clarke C, Luyt DK, Simpson H. Pediatr Pulmonol 1998; 26(4):256.

We investigated the outcome for a sample of children in whom recurrent cough was reported in the preschool years to determine 1) whether they shared the characteristics attributed to cough variant asthma, and 2) the proportion who developed classical wheezy asthma at follow-up during the early school years. A cohort of children identified as having recurrent cough in the preschool period was reassessed during the early school years. Previously identified asymptomatic preschool children who remained symptom-free provided a comparison group with respect to current respiratory symptoms, lung function, bronchial reactivity to inhaled methacholine, atopic status, peak flow variability, and recorded night cough. The response rate was modest, with 41% attending the follow-up study; information on current symptoms was available from a further 16%. Ascertainment of current symptoms showed that 70 of 125 (56.0% [95% CI 47.3–64.5%]) were symptom-free at follow-up, 46 (36.8% [28.7–45.5%]) continued to have recurrent cough in the absence of colds, and 9 (7.2% [3.6–12.8%]) reported recent attacks of wheeze. When comparing the 46 children whose recurrent cough persisted from the preschool period through to follow-up with subjects from the asymptomatic comparison group, the former had significantly more night cough (50.0% vs. 16.8%; $P< 0.01$), were more likely to be treated (10.9% vs. 1.7%; $P=0.01$), or were diagnosed (26.1% vs. 5.7%; $p < 0.001$) as asthmatic. They also showed greater bronchial reactivity than their asymptomatic counterparts (1.23 mg/mL vs. 3.35 mg/mL; $p=0.002$). Atopic status and other indices of lung function were similar between groups. We conclude that there are a group of children with long-term recurrent cough who display features consistent with a diagnosis of cough variant asthma, but at 2–4 years of follow-up, few progress to develop asthma characterized by wheeze.

Comparison of Lung Volume Measurements by Antero-Posterior Chest X-Ray Aand the SF6 Washout Technique in Mechanically Ventilated Infants—Thome U, Topfer A, Schaller P, Pohlandt F. Pediatr Pulmonol 1998; 26(4):265.

While anterior/posterior chest x-rays (CXR) are routinely performed to estimate lung volume (LV) and adjust ventilator settings, the precise measurement of LV requires additional sophistication. In 31 infants ventilated because of surfactant deficiency ($n=23$), bronchopulmonary dysplasia ($n=7$), or pulmonary hypoplasia ($n=1$) with either intermittent positive pressure ($n=18$) or high frequency oscillation ($n=13$) (gestational age 23–39 weeks (median 26 weeks); birthweight 550-2780 g (median 840 g); age at measurement 1–91 days (median 6 days); weight at study time (WST) 675-3000 g (median 938 g)), we investigated whether LV, as measured by the sulfur hexafluoride (SF6) washout technique, could by estimated from CXR by: 1) the sum (A+B) of the right (A) and left (B) lung fields areas; 2) the product (LxW) of the distances from the right apex to the right costophrenic angle (L) and between both costophrenic angles (W); 3) the diaphragm position relative to the posterior parts of the ribs (DP); and 4) the lung radiolucency (RL, grades 0–4). Correlations between A+B ($r=0.44$) or LxW ($r=0.37$) and LV were poor, but improved when A+B, LxW, and LV were normalized to WST: (A+B)/WST vs. LV/WST ($r=0.74$), and LxW/WST vs. LV/WST ($r=0.67$). DP ($r=0.13$) and RL (Spearman's rho=0.17) did not correlate with LV/WST. A multiple linear regression analysis led to the following best-fit equation: $LV/WST=2.58\ (A+B)/WST - 5.47\ DP + 42.2$ ($r=0.83$). We concluded that an estimate of LV from CXR lacked sufficient accuracy. DP and RL did not correlate with LV measured by SF6 washout.

Congenital Central Hypoventilation Syndrome: An Update—Gozal D. Pediatr Pulmonol 1998;26(4):273.

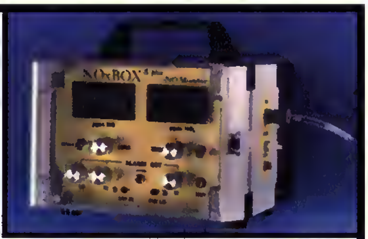
Awareness of the existence of CCHS has led to increasingly frequent reports of such patients from all over the world. However, the exact pathophysiologic mechanisms underlying the clinical manifestations of this congenital disease entity remain unknown. For the respiratory physiologist, CCHS can be viewed as an experiment of nature that provides an important and unique window into central cardiorespiratory regulation. For the pediatrician, CCHS children represent an unique clinical challenge in coordinating the diagnostic and therapeutic procedures required to enhance the patients' quality of life.

Liquid Ventilation in an Infant with Pulmonary Alveolar Proteinosis—Tsai WC, Lewis D, Nasr SZ, Hirschl RB. Pediatr Pulmonol 1998; 26(4):283.

Partial liquid ventilation (PLV) has been applied in various pulmonary diseases. We describe the use of partial liquid ventilation as a lavage method following normal saline (NS) lavage in an infant with pulmonary alveolar proteinosis (PAP) and severe hypoxemia. A 6 weeks old 3.4 kg former 36 weeks gestation boy on supplemental oxygen was transferred to our NICU with persistent tachypnea, dry cough, and increasing oxygen requirements. A lingular open lung biopsy revealed PAP. He developed progressive respiratory failure requiring ventilatory support, necessitating conventional NS lavage, followed by lung lavage with perflubron (LiquiVent; Alliance Pharmaceutical Corp. and Hoechst Marion Roussel) while on venovenous extracorporeal life support (ECLS). Lung lavage with NS and perflubron yielded minimal cloudy effluent. Gas exchange and pulmonary function deteriorated following NS lavage and attempts to discontinue ECLS were poorly tolerated. In contrast, tidal volume, P_{aO2}, and pulmonary compliance increased after PLV, while the (A-a) $D(O_2)$ decreased to a point where ECLS was no longer required. Once perflubron was added repeatedly to the ventilator circuit to correct for evaporation over the 4 days of PLV. Cardiovascular status remained stable for several days; however, eventually he required reinitiation of ECLS and more mechanical ventilatory support with each trial off ECLS. He was maintained on high pressures and F_{IO2} without any possibility to wean him from mechanical ventilation. Life support was withdrawn 1 month after admission. The survival from PAP in infants remains dismal, even with total lung NS lavage. While both NS and perflubron lavage in this patient were not effective in removing the proteinaceous alveolar debris, PLV following NS lavage was associated with an improvement in gas exchange and lung compliance.

Early Versus Late Surfactant Treatment in Preterm Infants of 27 to 32 Weeks' Gestational Age: A Multicenter Controlled Clinical Trial—Gortner L, Wauer RR, Hammer H, Stock GJ, Heitmann F, Reiter HL, et al. Pediatrics 1998;102(5):1153.

Objective. To investigate whether early (<1 hour after birth) surfactant administration would be superior to late treatment (2–6 hours after birth) in preterm infants. Study Design. Randomized controlled multicenter clinical trial. Pa-



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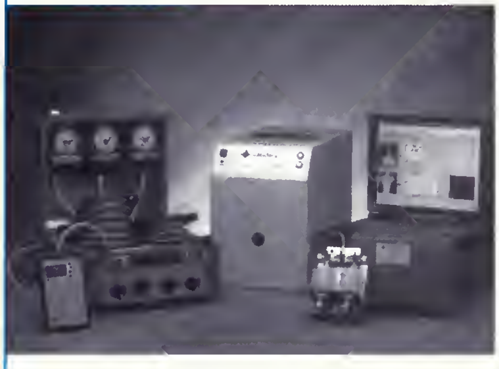

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tients and Methods. Prenatal randomization of all infants of 27 to 32 weeks' gestational age stratified by center after parental informed consent. Early treatment: 100 mg/kg body weight bovine surfactant (SF-RI1, Alveofact; Dr K. Thomae, Biberach, Germany) to infants requiring intubation after birth. Late treatment: identical dosage to infants requiring intubation up to 6 hours of age with the fraction of inspired oxygen >0.4 at 2 to 6 hours after birth. Primary endpoint: the time on mechanical ventilation. Main secondary endpoints: mortality, bronchopulmonary dysplasia, intraventricular hemorrhage ≤ grade III, and periventricular leukomalacia. Sample size calculation: at least 280 infants to prove superiority of either approach (alpha = 0.05; beta = 0.90). Results. Enrollment of 317 infants, 154 randomized to early surfactant treatment, 163 to late surfactant treatment. Study infants (all following data intent-to-treat groups: early versus late surfactant) were similar with respect to: gestational age, 29.5 ± 1.6 weeks versus 29.7 ± 1.6 weeks; birth weight, 1227 ± 367 g versus 1269 ± 334 g; and the rate of prenatal corticosteroids, 79.9% versus 72.8%. Duration of mechanical ventilation: 3 days (0–8) versus 2 days (0–6) (median, interquartile); further outcome variables: death or bronchopulmonary dysplasia (day 28) 25.9% versus 23.9%, mortality 3.2% versus 1.8%, intraventricular hemorrhage ≤ grade III 6.5% versus 3.7%, and periventricular leukomalacia 5.2% versus 5.5% not differing statistically. Conclusion. In preterm infants with a high rate of prenatal glucocorticoids, early surfactant administration was not found to be superior to late treatment in terms of relevant outcome variables.

Sleep and Daytime Behavior in Children with Obstructive Sleep Apnea and Behavioral Sleep Disorders—Owens J, Opipari L, Nobile C, Spirito A. Pediatrics 1998;102(5):1178.

Objective. The purpose of this study was: 1) to examine both bedtime sleep behaviors and daytime behaviors associated with daytime sleepiness in a group of children with a primary medical sleep disorder (obstructive sleep apnea syndrome [OSAS]) compared with a group of children with a primary behavioral sleep disorder (BSD) (limit setting sleep disorder or sleep onset association disorder); and 2) to investigate the impact of a comorbid BSD on sleep and daytime behavioral consequences of OSAS. Methods. Children referred to a pediatric sleep disorders clinic during a 3-year period with a primary diagnosis of either polysomnographically-confirmed OSAS (n = 100) or a BSD (n = 52) were compared on several parent report measures assessing the following domains: symptoms of sleep disordered breathing, other sleep behaviors (primarily parasomnias), bedtime behaviors, and externalizing daytime behavior problems. The OSAS sample was then divided into a pure OSAS group (n = 78) and an OSAS plus a behavioral sleep diagnosis group (n = 22) based on the presence or absence of delayed sleep onset and/or prolonged nightwakings and compared on the parent-report symptom domains. Results. Almost one-quarter of the OSAS group had clinically significant behavioral sleep problems, primarily bedtime resistance, in addition to OSAS. Bedtime resistance was associated with a significantly shortened sleep duration in both the BSD and OSAS-BSD groups. Although the OSAS-BSD group had less severe disease, as defined by polysomnographic variables, than the pure OSAS group, they were rated by their parents as having more daytime externalizing behavior problems associated with daytime sleepiness. Conclusions. The results of this study suggest that evaluation for comorbid BSD should be done in all children presenting with symptoms of OSAS. The coexistence of such BSDs may contribute significantly to sleep deprivation, and thus to behavioral manifestations of daytime sleepiness in these children.

Is the Asthma Quality of Life Questionnaire a Useful Measure for Low-Income Asthmatics?—Leidy NK, Chan KS, Coughlin C. Am J Respir Crit Care Med 1998;158(4):1082.

The purpose of this study was to evaluate the reliability and validity of the Asthma Quality of

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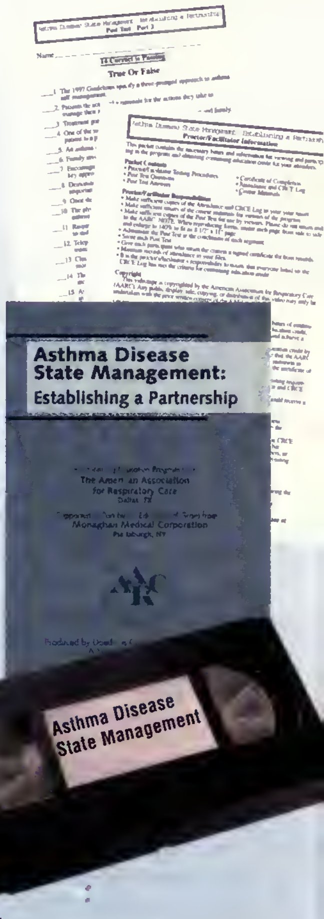
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Life Questionnaire (AQLQ) in a population-based sample of low-income adults with asthma. A total of 112 subjects (46 African American, 66 Caucasian; mean age = 33 ± 9 yr; 26% male) were recruited from the Baltimore County, Maryland and Atlanta, Georgia metropolitan areas. Internal consistency reliability (Cronbach's alpha) was high for the overall scale (0. 96); 2-wk reproducibility (intraclass correlation, ICC) was 0.82 (n = 38). Overall score was significantly correlated with FEV_1 percentage of predicted (r = 0.20), and the Asthma Disease Severity Scale (r = -0.38). Correlations between overall score and the SF-36 Physical Component Summary (r = 0.49), SF-36 Mental Component Summary (r = 0.37), Cantril's Ladder (r = 0.23), and the Health Utilities Index (r = 0.22) supported the validity of the AQLQ in this sample. Comparison of reliability and validity estimates across racial groups found few substantive differences. Internal consistency, reproducibility, and validity estimates found in this sample were consistent with those of a reliable and valid measure and were comparable to those found in other populations. These results suggest the AQLQ is a useful indicator of health- related quality of life in low-income asthmatics.

Infant and Maternal Outcomes in the Pregnancies of Asthmatic Women—Demissie K, Breckenridge MB, Rhoads GG. Am J Respir Crit Care Med 1998;158(4):1091.

We examined the relationship between infant and maternal outcomes and asthma complicating pregnancy, using historical cohort analysis of singleton live deliveries in New Jersey hospitals between 1989 and 1992 (n = 447,963). Subject mother-infant dyads were identified from linked birth certificate and maternal and newborn hospital claims data. Women with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code (493) for asthma (n = 2,289) were compared with a fourfold larger randomly selected control sample (n = 9,156) from the remaining pool of women. After controlling for the effects of important confounding variables, maternal asthma was associated with the following adverse infant outcomes: preterm infant (odds ratio [OR] = 1.36; 95% confidence interval [CI], 1.18 to 1.55), low birth weight (OR = 1. 32; 95% CI, 1.10 to 1.58), small-for-gestational age (OR = 1.26; 95% CI, 1.10 to 1.45), congenital anomalies (OR = 1.37; 95% CI, 1.12 to 1.68), and increased infant hospital length of stay (OR = 1.44; 95% CI, 1.25 to 1.65). The adverse maternal outcomes associated with maternal asthma were: pre-eclampsia (OR = 2.18; 95% CI, 1.68 to 2. 83), placenta previa (OR = 1.71; 95% CI, 1.05 to 2.79), cesarean delivery (OR = 1.62; 95% CI, 1.46 to 1.80), and increased maternal hospital length of stay (OR = 1.86; 95% CI, 1.60 to 2.15). The results emphasize the need for maternal asthma to be added to the list of conditions that increase the risk of adverse pregnancy outcomes.

Prediction of Clinical Severity and Outcome of Ventilator-Associated Pneumonia: Comparison of Simplified Acute Physiology Score with Systemic Inflammatory Mediators—Froon AHM, Bonten MJM, Gaillard CA, Greve JWM, Dentener MA, de LEEUW PW. Am J Respir Crit Care Med 1998;158(4):1026.

Systemic kinetics of three inflammatory mediators (bactericidal/permeability-increasing protein [BPI], soluble intercellular adhesion molecule [sICAM], and soluble E-selectin [sE-selectin]) were studied during the development of ventilator-associated pneumonia (VAP) (n = 42), diagnosed on quantitative cultures of bronchoscopic samples. From a pool of collected samples, nested samples were used to measure mediators on Days -4, -2, 0, and +2, relative to diagnosis. Correlations between systemic levels of mediators and clinical severity of infection (VAP with or without severe sepsis or septic shock) and patient outcome (mortality at Day 10 after diagnosis) were studied. Predictive values of inflammatory mediators were compared with daily Simplified Acute Physiology Score II (SAPS II) values and the logarithmic number of bacteria in bronchoscopic samples. During the development of VAP, increasing SAPS II scores and rising systemic mediator levels were only found in patients in whom VAP was accompanied with severe sepsis or septic shock. Values of SAPS II and plasma levels of BPI and sE-selectin, but not sICAM, increased from the day of diagnosis on in patients who died within 10 d of diagnosis. Systemic levels of inflammatory mediators did not better predict clinical severity or patient outcome than daily SAPS II scores. The logarithmic number of bacteria in bronchoscopic samples poorly correlated with circulating levels of inflammatory mediators, severity of infection, and patient outcome. Our findings show that a clinical scoring system (SAPS II score) is at least as good as a predictor for the clinical severity of infection and patient outcome, and provide new information on the kinetics of inflammatory mediators during the development of VAP.

Randomized Controlled Trial of Physician-Directed versus Respiratory Therapy Consult Service-Directed Respiratory Care to Adult Non-ICU Inpatients—Stoller JK, Mascha EJ, Kester L, Haney D. Am J Respir Crit Care Med 1998;158(4):1068.

Although current evidence suggests that respiratory care protocols can enhance allocation of respiratory care services while conserving costs, a randomized trial is needed to address shortcomings of available studies. We therefore conducted a randomized controlled trial comparing respiratory care for adult non-ICU inpatients directed by a Respiratory Therapy Consult Service (RTCS) versus respiratory care by managing physicians. Eligible subjects were adult non-ICU inpatients whose physicians had prescribed specific respiratory care services. Consecutive eligible patients were approached for consent, after which a blocked randomization strategy was used to assign patients to (1) Physician-directed respiratory care, in which the prescribed physician respiratory care orders were maintained (n = 74), or (2) RTCS-directed respiratory care, in which the physician's respiratory care orders were preempted by a respiratory care plan generated by the RTCS (n = 71). Specifically, these patients were evaluated by an RTCS therapist evaluator whose respiratory care plan was based on sign/symptom-based algorithms drafted to comply with the American Association for Respiratory Care (AARC) Clinical Practice Guidelines. Appropriateness of respiratory care orders was assessed as agreement between the prescribed respiratory care plan and an algorithm-based "standard care plan" generated by an expert therapist who was blind to the patient's actual orders. The compared groups were similar at baseline regarding demographic features, admission diagnostic category, smoking status, and Triage Score (mean, 3.8 ± 0.9 SD [RTCS] versus 3.7 ± 1.0). Similarly, no differences were observed between RTCS-directed and physician-directed respiratory care regarding hospital mortality rate (5.7 versus 5.6%), hospital length of stay (7.9 ± 9.0 versus 7.7 ± 7.3 d), total number of respiratory care treatments delivered (30.3 ± 30 versus 31.6 ± 30.5), or days requiring respiratory care (4.2 ± 5.2 versus 4.1 ± 3.6). Notably, using both a stringent (S) and a liberal (L) criterion for agreement, RTCS-directed respiratory care demonstrated better agreement with the "standard care plan" (82 ± 17% [S] and 86 ± 16% [L]) than did physician-directed respiratory care (64 ± 21% [S] and 72 ± 23% [L]) ($p < 0.001$). Finally, the true cost of respiratory care treatments was slightly lower with RTCS-directed respiratory care (mean, $235.70 versus $255.70/pt, p = 0.61). We conclude that (1) compared with physician-directed respiratory care, the RTCS prescribed a similar number and duration of respiratory care services at a slight savings (that did not achieve statistical significance) and without any increased adverse events; and (2) compared with physician-directed respiratory care, RTCS-directed respiratory care showed greater agreement with Clinical Practice Guideline-based algorithms.

Early Predictive Factors of Survival in the Acute Respiratory Distress Syndrome: A Multivariate Analysis—Monchi M, Bellenfant F, Cariou A, Joly LM, Thebert D, Laurent I, et al. Am J Respir Crit Care Med 1998;158(4):1076.

To identify the potential impact of novel therapeutic approaches, we studied the early predictive factors of survival at the onset of acute respiratory distress syndrome (ARDS) in a 24-bed medical ICU of an academic tertiary care hospital. Over a 48-mo period, a total of 3,511 adult patients were admitted and 259 mechanically ventilated patients met ARDS criteria, as defined by American-European consensus conference, i.e., bilateral pulmonary infiltrates and P_{aO2}/F_{IO2} lower than 200 without left atrial hypertension. These patients were randomly included in a developmental sample (177 patients) and a validation sample (82 patients). Demographic variables, hemodynamic and respiratory parameters, underlying diseases, as well as several severity scores (SAPS, SAPS-II, OSF) and Lung Injury Score (LIS) were collected. These variables were compared between survivors and nonsurvivors and entered into a stepwise logistic regression model to evaluate their independent prognostic roles. The overall mortality rate was 65%. SAPS-II, the severity of the underlying medical conditions, the oxygenation index (mean airway pressure x F_{IO2} x 100/ P_{aO2}), the length of mechanical ventilation prior to ARDS, the mechanism of lung injury, cirrhosis, and occurrence of right ventricular dysfunction were independently associated with an elevated risk of death. Model calibration was very good in the developmental and validation samples ($p = 0.84$ and $p = 0.72$, respectively), as was model discrimination (area under the ROC curves of 0.95 and 0.92, respectively). Thus, the prognosis of ARDS seems to be related to the triggering risk factor, the severity of the respiratory illness, and the occurrence of a right ventricle dysfunction, after adjustment for a general severity score.

A National Survey of End-of-Life Care for Critically Ill Patients—Prendergast TJ, Claessens MT, Luce JM. Am J Respir Crit Care Med 1998;158(4):1163.

In some intensive care units (ICUs), fewer patients who die now undergo attempts at cardiopulmonary resuscitation (CPR), and many more have life support actively withdrawn prior to death than did a decade ago. To determine the frequency of withdrawal of life support, we contacted every American postgraduate training program with significant clinical exposure to critical care medicine, asking them prospectively to classify patients who died into one of five mutually exclusive categories. We received data from 131 ICUs at 110 institutions in 38 states. There were 6,303 deaths, of which 393 patients were brain dead. Of the remaining 5,910 patients who died, 1,544 (23%) received full ICU care including failed cardiopulmonary resuscitation (CPR); 1,430 (22%) received full ICU care without CPR; 797 (10%) had life support withheld; and 2,139 (38%) had life support withdrawn. There was wide variation in practice among ICUs, with ranges of 4 to 79%, 0 to 83%, 0 to 67%, and 0 to 79% in these four categories, respectively. Variation was not related to ICU type, hospital type, number of admissions, or ICU mortality. We conclude that limitation of life support prior to death is the predominant practice in American ICUs associated with critical care training programs. There is wide variation in end-of-life care, and efforts are needed to understand practice patterns and to establish standards of care for patients dying in ICUs.

Analysis of Clinical Methods Used To Evaluate Dyspnea in Patients with Chronic Obstructive Pulmonary Disease—Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Am J Respir Crit Care Med 1998;158(4): 1185.

When dyspnea must be assessed clinically, there are three methods of assessment: the measurement of dyspnea with activities of daily living using clinical dyspnea ratings such as the modified Medical Research Council (MRC), the Baseline Dyspnea Index (BDI), and the Oxygen Cost Diagram (OCD); the measurement of dyspnea during exercise using the Borg scale; to assess the influence of dyspnea on health-related quality of life (HRQoL) using disease-specific questionnaires such as the St. George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ). The purpose of the present cross-sectional study was to clarify relationships between dyspnea ratings and HRQoL questionnaires by applying factor analysis. One hundred sixty-one patients with mild to severe COPD completed pulmonary function tests, progressive cycle ergometer testing for exercise capacity, assessment of dyspnea, HRQoL, anxiety, and depression. Factor analysis demonstrated that the MRC, BDI, OCD, and Activity of the SGRQ, and Dyspnea of the CRQ, were grouped into the same factor, and the frequency distribution histograms of these five measures showed virtually the same distribution. The Borg scale at the end of maximum exercise was found to be a different factor. The MRC, BDI, OCD, and Activity in the SGRQ, and Dyspnea in the CRQ demonstrated the same pattern of correlation with physiologic data, and they had significant relationships with FEV_1 (correlation coefficients [Rs] = 0.31 to 0. 48) and maximal oxygen uptake (Rs = 0.46 to 0.60). Disease-specific HRQoL questionnaires, the SGRQ and the CRQ, which contain a specific dimension for evaluating dyspnea, may be substituted for clinical dyspnea ratings in a cross-sectional assessment. Dyspnea rating at the end of exercise may provide further information regarding dyspnea.

Effect of Lung Volume Reduction Surgery on Gas Exchange and Pulmonary Hemodynamics at Rest and during Exercise—Oswald-Mammosser M, Kessler R, Massard G, Wihlm JM, Weitzenblum E, Lonsdorfer J. Am J Respir Crit Care Med 1998;158(4):1020.

Lung volume reduction surgery (LVRS) has become an extended surgery for emphysema in order to improve the dyspnea of severely affected patients. Because resection of lung areas may reduce the vascular bed, which is an important factor of pulmonary hypertension in emphysematous patients, especially during exercise, the aim of our study was to assess the outcome of pulmonary hemodynamics and gas exchange at rest and during exercise after LVRS. Nine patients had right heart catheterization before and 3 to 12 mo (mean, 4.5 mo) after LVRS. FEV_1 increased from 705 to 1,005 mL ($p < 0.05$) after LVRS. P_{aO2}, P_{aCO2} and mean pulmonary artery pressure (Ppa) did not change after LVRS, either at rest or during exercise. However, a significant overall decrease of the respiratory swings of the pulmonary artery diastolic pressure (DeltaPd) at rest (median value, from 12 to 8 mm Hg, $p < 0.01$) and during exercise (from 20 to 15 mm Hg, $p < 0.05$) was observed. There was a significant correlation between the change in resting Ppa (Ppa before minus Ppa after LVRS) and the change in resting DeltaPd ($r = 0.73$, $p < 0.03$), and also between the change in exercising Ppa and the change in resting DeltaPd ($r = 0.80$, $p < 0.02$). Significant correlations were also found between the change in exercising Ppa and the change in exercising P_{aO2} ($r = -0.70$, $p < 0.05$), and between the change in exercising Ppa and the change in exercising P_{aCO2} ($r = 0.76$, $p < 0.03$). We conclude that pulmonary hemodynamics in most cases are not impaired by LVRS either at rest or during exercise. The possible mechanisms influencing hemodynamics after a lung volume reduction procedure are discussed.

A New Method To Analyze Lung Compliance when Pressure-Volume Relationship Is Nonlinear—Nikischin W, Gerhardt T, Everett R, Bancalari E. Am J Respir Crit Care Med 1998;158(4):1052.

Changes in dynamic lung compliance during inspiration and expiration cannot be modeled accurately with conventional algorithms. We developed a simple method to analyze pressure-volume (P/V) relationships under condition of nonlinearity (APVNL) and tested it in a lung model with known resistance and nonlinear P/V relationship. In addition, pulmonary mechanics in 22 infants, 11 of them with nonlinear P/V relationships, were analyzed with the new method. The findings were compared with those obtained by a recently introduced algorithm, multiple linear regression analysis (MLR) of the equation of motion. The APVNL method described the changing compliance (C) of the lung model accurately, whereas the MLR method underestimated C especially in the first half of the breath. In infants the MLR method gave highly variable, often nonphysiological C values in the beginning of a breath. In contrast, the coefficient of variability of measurements obtained by the APVNL method was significantly smaller ($p < 0.02$), and the indices of model-fit showed better agreement between calculated and observed pressure than for the MLR method ($p < 0.02$). We conclude that the APVNL method accurately describes nonlinear P/V relationships present during spontaneous breathing or mechanical ventilation. The method may be helpful in identifying and preventing pulmonary overdistention.

Randomised Controlled Trial of Self-Supervised and Directly Observed Treatment of Tuberculosis—Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Lancet 1998; 352(9137):1340.

BACKGROUND: Tuberculosis is a major public-health problem in South Africa, made worse by poor adherence to and frequent interruption of treatment. Direct observation (DO) of tuberculosis patients taking their drugs is supposed to improve treatment completion and outcome. We compared DO with self-supervision, in which patients on the same drug regimen are not observed taking their pills, to assess the effect of each on the success of tuberculosis treatment. METHODS: We undertook an unblinded randomised controlled trial in two communities with large tuberculosis caseloads. The trial included 216 adults who started pulmonary tuberculosis treatment for the first time, or who had a second course of treatment (retreatment patients). No changes to existing treatment delivery were made other than randomisation. Analysis was by intention to treat. Individual patient data from the two communities were combined. FINDINGS: Treatment for tuberculosis was more successful among self-supervised patients (60% of patients) than among those on DO (54% of patients, difference between groups 6% [90% CI -5.1 to 17.0]). Retreatment patients had significantly more successful treatment outcomes if self-supervised (74% of patients) than on DO (42% of patients, difference between groups 32% [11%–52%]). INTERPRETATION: At high rates of treatment interruption, self-supervision achieved equivalent outcomes to clinic DO at lower cost. Self-supervision achieved better outcomes for retreatment patients. Supportive patient-carer relations, rather than the authoritarian surveillance implicit in DO, may improve treatment outcomes and help to control tuberculosis.

Intravenous Almitrine Bismesylate Reversibly Induces Lactic Acidosis and Hepatic Dysfunction in Patients with Acute Lung Injury—B'chir A, Mebazaa A, Losser MR, Romieu M, Payen D. Anesthesiology 1998;89(4):823.

BACKGROUND: Intravenous almitrine, which augments hypoxic pulmonary vasoconstriction, is used for short-term improvement of arterial oxygenation. However, recent research has suggested a potentially harmful effect on lactate metabolism and hepatic function. METHODS: Arterial oxygenation, hemodynamic parameters, plasma lactate, and hepatic function were monitored prospectively in 25 patients with acute lung injury (defined as a ratio of arterial oxygen pressure to inspiratory oxygen fraction ≤ 150 mm Hg) who where treated with intravenous almitrine. In 21 of 25 patients, acute lung injury was related to primary lung lesions, including pneumonia, postcardiosurgical atelectasis, and lung contusions. RESULTS: Intravenous almitrine increased the ratio of arterial oxygen pressure to inspiratory oxygen fraction from 93 ± 33 mm Hg to 207 ± 107 mm Hg (mean ± SD). In eight patients (three men), the plasma lactate concentration increased by an average of +3.5 ± 1.8 mM, and the pH and bicarbonate concentration both decreased during the first 24 h of treatment. In this group of patients, the total bilirubin concentration was elevated before almitrine administration, and the results of other hepatic function tests, such as aspartate aminotransferase, alanine aminotransferase, and prothrombin time, were altered by almitrine administration. Therefore, intravenous almitrine was discontinued. Lactic acidosis and hepatic dysfunction improved. In the other 17 patients (14 men), the plasma lactate concentration and the hepatic function tests remained unaltered during intravenous almitrine therapy for > 60 h. Univariate and multivariate analyses revealed that an abnormal plasma concentration of total bilirubin before almitrine administration and female gender were the two factors significantly linked with lactic acidosis during almitrine infusion. CONCLUSIONS: This study confirms that intravenous almitrine greatly improves arterial oxygenation in patients with acute lung injury but may also induce lactic acidosis and hepatic dysfunction. The coexistence of lactic acidosis and hepatic dysfunction in the same patients strongly suggests that the liver is the primary source of intravenous almitrine-induced lactic acidosis.

Effects of Respiratory Alkalosis and Acidosis on Myocardial Blood Flow and Metabolism in Patients with Coronary Artery Disease—Kazmaier S, Weyland A, Buhre W, Stephan H, Rieke H, Filoda K, Sonntag H. Anesthesiology 1998;89(4):831.

BACKGROUND: Variation of the arterial carbon dioxide partial pressure (P_{aCO_2}) is not uncommon in anesthetic practice. However, little is known about the myocardial consequences of respiratory alkalosis and acidosis, particularly in patients with coronary artery disease. The aim of the current study was to investigate the effects of variation in P_{aCO_2} on myocardial blood flow (MBF), metabolism, and systemic hemodynamics in patients before elective coronary artery bypass graft surgery. METHODS: In 10 male anesthetized patients, measurements of MBF, myocardial contractility, metabolism, and systemic hemodynamics were made in a randomized sequence at P_{aCO_2} levels of 30, 40, and 50 mm Hg, respectively. The MBF was measured using the Kety-Schmidt technique with argon as a tracer. End-diastolic left ventricular pressure and the maximal increase of left ventricular pressure were assessed using a manometer-tipped catheter. RESULTS: The cardiac index significantly changed with varying P_{aCO_2} levels (hypocapnia, - 9%; hypercapnia, 13%). This reaction was associated with inverse changes in systemic vascular resistance index levels. The MBF significantly increased by 15% during hypercapnia, whereas no change was found during hypocapnia. Myocardial oxygen and glucose uptake and the maximal increase of left ventricular pressure were not affected by varying P_{aCO_2} levels. CONCLUSIONS: In anesthetized patients with coronary artery disease, short-term variations in P_{aCO_2} have significant effects on MBF but do not influence global myocardial oxygen and glucose uptake. Changes in systemic hemodynamics associated with respiratory alkalosis and acidosis are caused by changes in systemic vascular resistance rather than by alterations in myocardial contractility.

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Influence of Mechanical Ventilation On Blood Lactate In Patients With Acute Respiratory Failure—Gil A, Carrizosa F, Herrero A, Martin J, Gonzalez J, Jareno A, Rivero J. Intensive Care Med 1998;24(9):924.

OBJECTIVES: To determine whether mechanical ventilation (MV) may affect blood lactate concentration in patients with acute respiratory failure. DESIGN: Prospective observational study with follow-up to hospital discharge. SETTING: A 17-bed medical and coronary intensive care unit in a 650-bed general hospital. PATIENTS: 55 adult patients mechanically ventilated for acute respiratory failure between May 1996 and April 1997 were recruited. MEASUREMENTS AND RESULTS: Arterial blood samples for determination of plasma lactate and blood gas analysis were taken just before tracheal intubation on spontaneous breathing, and 20 and 60 min after the initiation of controlled MV. Cuff systemic arterial pressure was measured before tracheal intubation and every 10 min during the first h of MV. Hyperlactatemia (arterial blood lactate $\geq$ 2 mmol/l) was present in 21 of the 55 patients studied. After 20 min of MV, there was a decrease in blood lactate from 4.74 ± 1.78 to 3.07 ± 1.69 mmol/l ($p < 0.01$); 40 min later there was a further decrease to 2.63 ± 1.35 mmol/l ($p < 0.05$). The decrease in blood lactate was also observed in those patients who after starting MV developed systemic arterial hypotension ($p < 0.01$). In patients with a normal lactate concentration at the entry to the study, lactate remained the same after 60 min on MV (NS). CONCLUSIONS: Controlled MV decreases substantially the severity of hyperlactatemia in patients with acute respiratory failure, and any adverse circulatory effects of MV do not alter this beneficial outcome.

Work of Breathing, Inspiratory Flow Response, and Expiratory Resistance during Continuous Positive Airway Pressure with the Ventilators EVITA-2, EVITA-4 and SV 300—Calzia E, Lindner KH, Stahl W, Martin A, Radermacher P, Georgieff M. Intensive Care Med 1998;24(9):931.

OBJECTIVE: To analyze work of breathing (WOB) imposed by the respirators EVITA-2, EVITA-4 (Dragerwerk, Lubeck, Germany) and SV 300 (Siemens-Elema, Sweden) as well as inspiratory flow response and expiratory flow resistance during continuous positive airway pressure (CPAP). DESIGN: Five study conditions on a lung model (CPAP at 0, 5, and 10 mbar, CPAP 5 mbar plus pressure support 2 mbar with both EVITA models, and CPAP 5 mbar with decreasing levels of flow and pressure trigger sensitivity with the SV 300) and three randomized study conditions in nine patients recovering from open heart surgery (condition A: EVITA-2, CPAP 5 mbar; condition B: SV 300, CPAP 5 mbar, flow trigger; condition C: SV 300, pressure trigger-4 mbar). SETTING: University hospital intensive care unit and laboratory of pulmonary physiology. MEASUREMENTS AND RESULTS: At each study condition we measured WOB, pressure-time product (PTP), WOB and PTP imposed (WOBimposed and PTPimposed), tidal volume, minute ventilation, respiratory rate, inspiratory trigger time, trigger pressure, trigger PTP, duration of inspiration, mean and peak inspiratory flow, and the delay from the onset of inspiration to peak inspiratory flow. Since the SV 300 automatically generates an additional pressure support of 2 cm H_2O PTP, WOB, WOBimposed, and PTPimposed were higher with the EVITA-2 and EVITA-4 regardless of the trigger sensitivity set on the SV 300. The difference was neutralized with both types of EVITA ventilator by adding 2 mbar of pressure support during CPAP in order to achieve comparable conditions. Inspiratory flow response was faster with both EVITA models, expiratory flow resistance was higher with the SV 300. Decrements of trigger sensitivity with the SV 300 accelerated the flow response. CONCLUSIONS: Under similar conditions, no difference in WOBimposed was observed, although inspiratory flow response and expiratory flow resistance differed substantially between the three ventilators tested. Trigger sensitivity plays a minor role in determining PTP and WOB but has major influence on flow.

A Profile of European ICU Nursing—Depasse B, Pauwels D, Somers Y, Vincent JL. Intensive Care Med 1998;24(9):939.

OBJECTIVE: To evaluate major similarities and major differences between Western European countries in intensive care unit (ICU) nurse staffing, education, training, responsibilities, and initiative. DESIGN: A questionnaire was sent to Western European doctor members of the European Society of Intensive Care Medicine, to be passed on to the nurse-in-charge of their ICU. RESULTS: 156 completed questionnaires were analyzed: 49% were from university hospitals, 26% from university-affiliated hospitals, and 25% from community hospitals; 42% of the hospitals had more than 700 beds, 67% of the ICUs had between 6 and 12 beds, and 54% were mixed medical-surgical units. Among British units, 79% had more than three full-time nursing equivalents (FTE) per ICU bed, while in Sweden 75% of units had less than two FTE/ICU bed. University hospitals had more nursing staff per bed than community hospitals. As regards training, 33% of nurses followed a training course before starting work on the ICU and 64% after starting on the unit, and 85% had easy access to continuing education, particularly in the university hospitals. In an emergency, more than 70% of nurses regularly initiated oxygen administration, mask ventilation, or cardiac massage. In Sweden 100% of nurses and in Switzerland 91% of nurses regularly inserted peripheral intravenous catheters, but only 7% of German nurses did. No German nurses and only 12% of British nurses regularly performed arterial puncture, but in Sweden 75% of nurses regularly did. CONCLUSION: Even though the number of participants were limited, our questionnaire revealed variations in nurse staffing patterns among European countries and in their systems of training and education. Nurse autonomy also varies widely between countries.

The Use of Intensive Care Information Systems Alters Outcome Prediction—Bosman RJ, van Straaten HM, Zandstra DF. Intensive Care Med 1998;24(9):953.

OBJECTIVE: To study the effect of using an Intensive Care Information System (ICIS) on severity scores and prognostic indices: Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II), and Mortality Probability Models II (MPM II). DESIGN: Prospective pilot study. SETTING: A 20-bed medical-surgical intensive care unit (ICU) in a teaching hospital. PATIENTS: 50 consecutive adult patients admitted to the ICU on a bed equipped with an ICIS. INTERVENTIONS: None. MEASUREMENTS AND RESULTS: In each patient all the physiologic variables, as required by the severity scores, were both manually charted and recorded by ICIS. ICIS registration resulted in the extraction of more abnormal values for all physiologic variables (except temperature): $p < 0.05$. Higher severity scores and mortality prediction were achieved by using ICIS charting: predicted mortality increased by 15% for APACHE II compared to manual charting, 25% for SAPS II, and 24% for MPM0. ICIS charting resulted in higher severity scores and mortality prediction for 29 of the 50 patients using APACHE II with a mean increase in mortality prediction in this subgroup of 27%. In the case of SAPS II, ICIS charting resulted in higher scores in 23 of the 50 patients and in the case of MPM0 in 13 patients, the mean increase in mortality in these subgroups being 64 and 148%, respectively. CONCLUSIONS: The use of ICIS charting to acquire the most abnormal physiologic values for severity scores and the derived prognostic indices results in a higher mortality prediction. Comparison of groups of patients and/or ICUs based on severity scores is impossible without standardization of data collection. The mortality prediction models have to be revalidated for the use of ICIS charting. While awaiting this, we suggest that every patient record in local regional, national, or international ICU databases should be marked as being recorded by manual or by ICIS charting.

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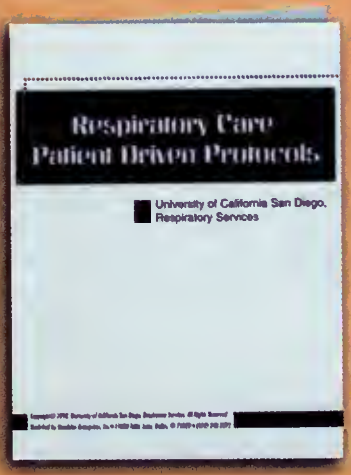

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Respiratory Distress Syndrome—Masclans JR, Iglesia R, Bermejo B, Pico M, Rodriguez-Roisin R, Planas M. Intensive Care Med 1998; 24(9):918.

OBJECTIVE: To investigate the gas exchange and pulmonary haemodynamic responses to two different intravenous fat emulsions in patients with acute respiratory distress syndrome (ARDS). DESIGN: Prospective, randomized, double-blind, placebo-controlled study. SETTING: Intensive care unit in a university-affiliated hospital. PATIENTS: 21 patients with ARDS [mean age, 57 ± 3 (SEM) years; Acute Physiology and Chronic Health Evaluation II, 20 ± 3; Murray's score, 2.85 ± 0.12] consecutively admitted. INTERVENTIONS: Patients were assigned to three groups ($n = 7$ each): group A (LCT) received long-chain triglycerides (20% LCT), group B (MCT/LCT), medium-chain triglycerides/long-chain triglycerides (20% MCT/LCT: 50/50) and group C placebo (0.9% sodium chloride, NaCl). The infusion was always given at the rate of 2 mg/kg min over a total period of 12 h, with a volume infusion of 500 mL in each group. MEASUREMENTS: Data were collected before, immediately after and 12 h after infusion ceased. Pulmonary and systemic haemodynamic and gas exchange variables were measured at each time point. Serum triglyceride cholesterol, and non-esterified fatty acids levels were measured. RESULTS: During LCT infusion, cardiac output, oxygen consumption and oxygen delivery increased (all $p < 0.05$), whereas pulmonary haemodynamics, arterial oxygen tension, mixed venous partial pressure of oxygen and venous admixture ratio remained essentially unaltered. No changes were observed following MCT/LCT infusion. CONCLUSIONS: The administration of LCT emulsion given at a slow rate did not alter arterial oxygenation because of the beneficial effect of a high cardiac output, hence offsetting the detrimental effect of increased O_2 consumption.

Trends in Alternative Medicine Use in the United States, 1990–1997: Results of a Follow-Up National Survey—Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. JAMA 1998;280(18):1569.

CONTEXT: A prior national survey documented the high prevalence and costs of alternative medicine use in the United States in 1990. OBJECTIVE: To document trends in alternative medicine use in the United States between 1990 and 1997. DESIGN: Nationally representative random household telephone surveys using comparable key questions were conducted in 1991 and 1997 measuring utilization in 1990 and 1997, respectively. PARTICIPANTS: A total of 1539 adults in 1991 and 2055 in 1997. MAIN OUTCOMES MEASURES: Prevalence, estimated costs, and disclosure of alternative therapies to physicians. RESULTS: Use of at least 1 of 16 alternative therapies during the previous year increased from 33.8% in 1990 to 42.1% in 1997 ($p \leq .001$). The therapies increasing the most included herbal medicine, massage, megavitamins, self-help groups, folk remedies, energy healing, and homeopathy. The probability of users visiting an alternative medicine practitioner increased from 36.3% to 46.3% ($p = .002$). In both surveys alternative therapies were used most frequently for chronic conditions, including back problems, anxiety, depression, and headaches. There was no significant change in disclosure rates between the 2 survey years; 39.8% of alternative therapies were disclosed to physicians in 1990 vs 38.5% in 1997. The percentage of users paying entirely out-of-pocket for services provided by alternative medicine practitioners did not change significantly between 1990 (64.0%) and 1997 (58.3%) ($p=.36$). Extrapolations to the US population suggest a 47.3% increase in total visits to alternative medicine practitioners, from 427 million in 1990 to 629 million in 1997, thereby exceeding total visits to all US primary care physicians. An estimated 15 million adults in 1997 took prescription medications concurrently with herbal remedies and/or high-dose vitamins (18.4% of all prescription users). Estimated expenditures for alternative medicine professional services increased 45.2% between 1990 and 1997 and were conservatively estimated at $21.2 billion in 1997, with at least $12.2 billion paid out-of-pocket. This exceeds the 1997 out-of-pocket expenditures for all US hospitalizations. Total 1997 out-of-pocket expenditures relating to alternative therapies were conservatively estimated at $27.0 billion, which is comparable with the projected 1997 out-of-pocket expenditures for all US physician services. CONCLUSIONS: Alternative medicine use and expenditures increased substantially between 1990 and 1997, attributable primarily to an increase in the proportion of the population seeking alternative therapies, rather than increased visits per patient.

Kinetics of Oxygen Uptake at the Onset of Exercise in Boys and Men—Hebestreit H, Kriemler S, Hughson RL, Bar-Or O. J Appl Physiol 1998;85(5):1833.

The objective of this study was to compare the O_2 uptake (VO_2) kinetics at the onset of heavy exercise in boys and men. Nine boys, aged 9–12 yr, and 8 men, aged 19–27 yr, performed a continuous incremental cycling task to determine peak VO_2 (VO_2 peak). On 2 other days, subjects performed each day four cycling tasks at 80 rpm, each consisting of 2 min of unloaded cycling followed twice by cycling at 50% VO_2 peak for 3.5 min, once by cycling at 100% VO_2 peak for 2 min, and once by cycling at 130% VO_2 peak for 75 s. O_2 deficit was not significantly different between boys and men (respectively, 50% VO_2 peak task: 6.6 ± 11.1 vs. 5.5 ± 7.3 $mL \cdot min^{-1} \cdot kg^{-1}$; 100% VO_2 peak task: 28.5 ± 8.1 vs. 31.8 ± 6.3 $mL \cdot min^{-1} \cdot kg^{-1}$; and 130% VO_2 peak task: 30.1 ± 5.7 vs. 35.8 ± 5.3 $mL \cdot min^{-1} \cdot kg^{-1}$). To assess the kinetics, phase I was excluded from analysis. Phase II VO_2 kinetics could be described in all cases by a monoexponential function. ANOVA revealed no differences in time constants between boys and men (respectively, 50% VO_2 peak task: 22. 8 ± 5.1 vs. 26.4 ± 4.1 s; 100% VO_2 peak task: 28.0 ± 6.0 vs. 28.1 ± 4.4 s; and 130% VO_2 peak task: 19.8 ± 4.1 vs. 20.7 ± 5.7 s). In conclusion, O_2 deficit and fast-component VO_2 on-transients are similar in boys and men, even at high exercise intensities, which is in contrast to the findings of other studies employing simpler methods of analysis. The previous interpretation that children rely less on nonoxidative energy pathways at the onset of heavy exercise is not supported by our findings.

Fuel Metabolism in Men and Women during and after Long-Duration Exercise—Horton TJ, Pagliassotti MJ, Hobbs K, Hill JO. J Appl Physiol 1998;85(5):1823.

This study aimed to determine gender-based differences in fuel metabolism in response to long-duration exercise. Fuel oxidation and the metabolic response to exercise were compared in men ($n = 14$) and women ($n = 13$) during 2 h (40% of maximal O_2 uptake) of cycling and 2 h of postexercise recovery. In addition, subjects completed a separate control day on which no exercise was performed. Fuel oxidation was measured using indirect calorimetry, and blood samples were drawn for the determination of circulating substrate and hormone levels. During exercise, women derived proportionally more of the total energy expended from fat oxidation (50.9 ± 1.8 and 43.7 ± 2.1% for women and men, respectively, $p < 0.02$), whereas men derived proportionally more energy from carbohydrate oxidation (53.1 ± 2.1 and 45.7 ± 1.8% for men and women, respectively, $p < 0.01$). These gender-based differences were not observed before exercise, after exercise, or on the control day. Epinephrine ($p < 0.007$) and norepinephrine ($p < 0.0009$) levels were significantly greater during exercise in men than in women (peak epinephrine concentrations: 208 ± 36 and 121 ± 15 pg/mL in men and women, respectively; peak norepinephrine concentrations: 924 ± 125 and 659 ± 68 pg/mL in men and women, respectively). As circulating glycerol levels were not different between the two groups, this suggests that women may be more sensitive to the lipolytic action of the catecholamines. In conclusion, these data support the view that different priorities are placed on lipid and carbohydrate oxidation during exercise in men and women and that these gender-based differences extend to the catecholamine response to exercise.

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Alveolar Oxygen Uptake and Femoral Artery Blood Flow Dynamics in Upright and Supine Leg Exercise in Humans—MacDonald MJ, Shoemaker JK, Tschakovsky ME, Hughson RL. J Appl Physiol 1998;85(5):1622.

We tested the hypothesis that the slower increase in alveolar oxygen uptake (VO_2) at the onset of supine, compared with upright, exercise would be accompanied by a slower rate of increase in leg blood flow (LBF). Seven healthy subjects performed transitions from rest to 40-W knee extension exercise in the upright and supine positions. LBF was measured continuously with pulsed and echo Doppler methods, and VO_2 was measured breath by breath at the mouth. At rest, a smaller diameter of the femoral artery in the supine position ($p < 0.05$) was compensated by a greater mean blood flow velocity (MBV) ($p < 0.05$) so that LBF was not different in the two positions. At the end of 6 min of exercise, femoral artery diameter was larger in the upright position and there were no differences in VO_2, MBV, or LBF between upright and supine positions. The rates of increase of VO_2 and LBF in the transition between rest and 40 W exercise, as evaluated by the mean response time (time to 63% of the increase), were slower in the supine [$VO_2 = 39.7 \pm 3.8$ (SE) s, LBF = 27.6 ± 3.9 s] than in the upright positions ($VO_2 = 29.3 \pm 3.0$ s, LBF = 17.3 ± 4.0 s; $p < 0.05$). These data support our hypothesis that slower increases in alveolar VO_2 at the onset of exercise in the supine position are accompanied by a slower increase in LBF.

Inspiratory and Expiratory Patterns of the Pectoralis Major Muscle during Pulmonary Defensive Reflexes—Bolser DC, Reier PJ. J Appl Physiol 1998;85(5):1786.

Experiments were conducted to determine the discharge pattern of the pectoralis major muscle during pulmonary defensive reflexes in anesthetized cats ($n = 15$). Coughs and expiration reflexes were elicited by mechanical stimulation of the intrathoracic trachea or larynx. Augmented breaths occurred spontaneously or were evoked by the same mechanical stimuli. Electromyograms (EMGs) were recorded from the diaphragm, rectus abdominis, and pectoralis major muscles. During augmented breaths, the pectoralis major had inspiratory EMG activity similar to that of the diaphragm, but during expiration reflexes the pectoralis major also had purely expiratory EMG activity similar to the rectus abdominis. During tracheobronchial cough, the pectoralis major had an inspiratory pattern similar to that of the diaphragm in 10 animals, an expiratory pattern similar to that of the rectus abdominis in 3 animals, and a biphasic pattern in 2 animals. The pectoralis major was active during both the inspiratory and expiratory phases during laryngeal cough. We conclude that, in contrast to the diaphragm or rectus abdominis muscles, the pectoralis major is active during both inspiratory and expiratory pulmonary defensive reflexes.

Effects of Inspiratory and Expiratory Positive Pressure Difference on Airflow Dynamics during Sleep—Series F, Marc I. J Appl Physiol 1998;85(5):1855.

We measured the effects of dissociating inspiratory and expiratory positive pressure (PI and PE, respectively) on the inspiratory flow limitation pattern and on genioglossus (GG) activity in nine sleep apnea patients. Measurements were made at two different levels of PI with stepwise increases in PE. Flow-limited breaths were observed during each recording session. In six of nine subjects, maximal inspiratory flow (VImax) was correlated with the difference between PI and PE (correlations were negative in 5 subjects, positive in 1 subject). In three other patients, VImax was not influenced by the amount of pressure difference. A positive relationship between tonic and/or phasic GG electromyographic activities and PI-PE difference was observed at least at one PI level in all patients. This correlation was observed independently of the presence or absence of any relationship between VImax and the amount of pressure difference. Our results suggest that increasing the PI-PE difference (i.e., decreasing PE) may be associated with a significant worsening in inspiratory flow limitation and that the VImax-pressure difference behavior is not dependent on the GG electromyographic-pressure response.

Human Ventilatory Response to CO_2 after 8 H of Isocapnic or Poikilocapnic Hypoxia—Fatemian M, Robbins PA. J Appl Physiol 1998; 85(5):1922.

During ventilatory acclimatization to hypoxia (VAH), the relationship between ventilation (VE) and end-tidal PCO_2 ($P_{ET}CO_2$) changes. This study was designed to determine 1) whether these changes can be seen early in VAH and 2) if these changes are present, whether the responses differ between isocapnic and poikilocapnic exposures. Ten healthy volunteers were studied by using three 8-h exposures: 1) isocapnic hypoxia (IH), end-tidal PO_2 ($P_{ET}O_2$) = 55 Torr and $P_{ET}CO_2$ held at the subject's normal prehypoxic value; 2) poikilocapnic hypoxia (PH), $P_{ET}O_2$ = 55 Torr; and 3) control (C), air breathing. The VE-$P_{ET}CO_2$ relationship was determined in hyperoxia ($P_{ET}O_2$ = 200 Torr) before and after the exposures. We found a significant increase in the slopes of VE-$P_{ET}CO_2$ relationship after both hypoxic exposures compared with control (IH vs. C, $p < 0.01$; PH vs. C, $p < 0.001$; analysis of covariance with pairwise comparisons). This increase was not significantly different between protocols IH and PH. No significant changes in the intercept were detected. We conclude that 8 h of hypoxia, whether isocapnic or poikilocapnic, increases the sensitivity of the hyperoxic chemoreflex response to CO_2.

Idiopathic Pulmonary Fibrosis: Current Concepts—Ryu JH, Colby TV, Hartman TE. Mayo Clin Proc 1998;73(11):1085.

Idiopathic pulmonary fibrosis (IPF) is generally defined as a progressive, fibrosing inflammatory disease of the lung parenchyma of unknown cause. It is characterized by slowly increasing dyspnea, diffuse interstitial lung infiltrates, restrictive lung dysfunction, and impaired gas exchange. Ultimately, it is fatal in most patients, and treatment options remain unsatisfactory. The advent of high-resolution computed tomography of the chest and modifications in the histopathologic classification of interstitial pneumonias have reshaped the concept of IPF. Although initially thought to be a relatively specific clinicopathologic entity, it seems likely that IPF as previously defined is a heterogeneous disorder consisting of several clinicopathologic entities with differing histopathologic patterns, clinical course, response to therapy, and prognosis. The most common histologic pattern in cases previously defined as IPF is usual interstitial pneumonia, which is associated with a median survival of less than 3 years. For accurate prognosis and optimal management of patients, the clinician should attempt to be as precise as possible in distinguishing various clinicopathologic entities that have been included under the clinical heading of IPF. In the future, we recommend that the use of the term "idiopathic pulmonary fibrosis" be restricted to patients with usual interstitial pneumonia and that clinicians recognize the fact that other idiopathic interstitial pneumonias do not have the same prognostic effect traditionally ascribed to IPF.

Measurement of Pulmonary Resistance and Dynamic Compliance with Airway Obstruction—Officer TM, Pellegrino R, Brusasco V, Rodarte JR. J Appl Physiol 1998;85(5):1982.

We compared four algorithms by using least squares regression for determination of pulmonary resistance and dynamic elastance in subjects with emphysema, normal subjects, and subjects with asthma before and after bronchoconstriction. The four methods evaluated include 1) a single resistance and elastance, 2) separate resistances and elastances for each half breath, 3) separate inspiratory and expiratory resistances with a single elastance, and 4) separate inspiratory and expiratory resistances, an expiratory volume interaction term, and a single elastance. All methods gave comparable results in normal and asthmatic subjects. We found expiratory resistance was larger than inspiratory resistance in normal and asthmatic subjects during control conditions, but inspiratory resistance was higher than expiratory resistance in subjects who experienced severe bronchoconstriction in response to methacholine. In subjects who are flow limited, method 2 gives a higher inspiratory resistance than would be computed by assuming that the elastic pressure-volume curve passes through the zero-flow points. Methods 1 and 3 overestimate dynamic elastance and inspiratory resistance. Method 4 appears to identify flow limitation and dynamic hyperinflation and gives a good measure of inspiratory resistance and dynamic elastance.

Analysis of Forced Expiratory Maneuvers from Raised Lung Volumes in Preterm Infants—Henschen M, Stocks J, Hoo AF, Dixon P. J Appl Physiol 1998;85(5):1989.

During recent years it has been suggested that forced expiratory measurements, derived from a lung volume set by a standardized inflation pressure, are more reproducible than those attained during tidal breathing when the rapid thoracoabdominal compression technique is used in infants. The aim of this study was to evaluate the feasibility of obtaining measurements from raised lung volumes in unsedated preterm infants. Measurements were made in 18 infants (gestational age 26–35 wk, postnatal age 1–10 wk, test weight 1.4–3. 5 kg). Several inflations [1.5–2.5 kPa (15–25 cm H_2O)] were used to briefly inhibit respiratory effort before the rapid thoracoabdominal compression was performed. Conventional analysis of flows and volumes at fixed times and percentages of the forced expiration resulted in a relatively high variability in this population. However, by using the elastic equilibrium point (i.e., the passively determined lung volume, derived from passive expirations before the forced expiration) as a volume landmark, it was feasible to achieve reproducible results in unsedated preterm infants, despite their strong respiratory reflexes and rapid respiratory rates. Because this approach is independent of changes in expiratory time, expired volume, or applied pressures, it may facilitate investigation of the effects of growth, development, and disease on airway function in infants, particularly during the first weeks of life, when conventional analysis of forced expirations may be inappropriate.

Does Norepinephrine Modify the Effects of Inhaled Nitric Oxide in Septic Patients with Acute Respiratory Distress Syndrome?—Papazian L, Bregeon F, Gaillat F, Kaphan E, Thirion X, Saux P, et al. Anesthesiology 1998; 89(5):1089.

Hypoxia-related pulmonary vasoconstriction enhanced by norepinephrine could be deleterious in patients with the acute respiratory distress syndrome (ARDS) and sepsis. A prospective study compared the effects of nitric oxide on cardiorespiratory parameters, including the evaluation of right ventricular function in patients with ARDS and sepsis who were receiving or not receiving norepinephrine. METHODS: During a 15-month period, 27 patients with ARDS and sepsis were prospectively investigated (group 1: 15 patients not receiving norepinephrine; group 2: 12 patients receiving norepinephrine). Right ventricular ejection fraction was measured by thermodilution. After baseline measurements, nitric oxide was administered at increasing inspiratory concentrations. RESULTS: The ratio of oxygen tension in arterial blood to the fractional concentration of oxygen in inspired gas increased in the two groups. After logarithmic transformation of the data, an analysis of variance was performed that did not show any difference between the two groups. A dose-dependent decrease in mean pulmonary arterial pressure was observed in the two groups. This decrease and the increase in right ventricular ejection fraction induced by inhaled nitric oxide were more marked when patients received norepinephrine ($p < 0.0001$). CONCLUSION: Norepinephrine did not influence the beneficial effects of inhaled nitric oxide administered to patients with ARDS and sepsis on oxygenation.

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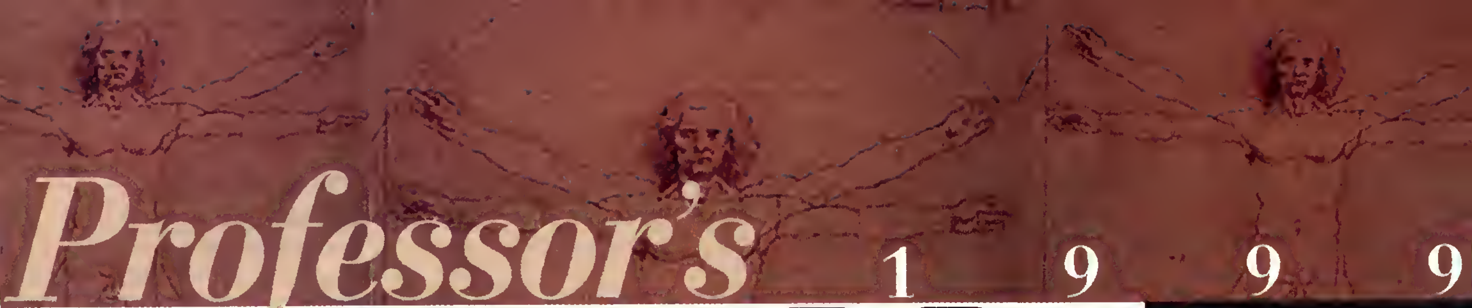
Cardiovascular and Valsalva Responses during Parabolic Flight—Schlegel TT, Benavides EW, Barker DC, Brown TE, Harm DL, DeSilva SJ, Low PA. J Appl Physiol 1998;85(5):1957.

We investigated the integrated cardiovascular responses of 15 human subjects to the acute gravitational changes (micro- and hypergravity portions) of parabolic flight. Measurements were made with subjects quietly seated and while subjects performed controlled Valsalva maneuvers. During quiet, seated, parabolic flight, mean arterial pressure increased during the transition into microgravity but decreased as microgravity was sustained. The decrease in mean arterial pressure was accompanied by immediate reflexive increases in heart rate but by absent (or later-than-expected) reflexive increases in total vascular resistance. Mean arterial pressure responses in Valsalva phases III, III, and IV were accentuated in hypergravity relative to microgravity ($p < 0.01$, $p < 0.01$, and $p < 0.\ 05$, respectively), but accentuations differed qualitatively and quantitatively from those induced by a supine-to-seated postural change in 1 G. This study is the first systematic evaluation of temporal and Valsalva-related changes in cardiovascular parameters during parabolic flight. Results suggest that arterial baroreflex control of vascular resistance may be modified by alterations of cardiopulmonary, vestibular, and/or other receptor activity.



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INHALED NITRIC OXIDE

Part I of Two Special Issues

Containing the manuscripts and discussions from the Journal Conference held September 11-13, 1998, in Banff, Alberta, Canada

This Journal Conference was made possible by educational grants to the

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Conference faculty members—front row, from left: Ronald G Pearl MD PhD, Richard D Branson RRT, Luca M Bigatello MD, Dean R Hess PhD RRT FAARC, Thomas E Stewart MD, William E Hurford MD. Back row, from left: C Alvin Head RRT RPFT MD, John Thompson RRT, Jesse D Roberts Jr MD, Richard N Channick MD, George F Rich MD PhD, Herwig Gerlach MD. Not pictured, Emile A Bacha MD.

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Dear Reader:

In 1982 the journal RESPIRATORY CARE published the proceedings from the first state-of-the-art conference presented by the American Association for Respiratory Care and the journal. This issue contains the proceeding from the 22nd conference held since 1982, (18 state-of-the-art conferences and 4 consensus conferences).

1999 – *Artificial Airways* (June and July, Volume 44, Numbers 6 and 7)
1999 – *Inhaled Nitric Oxide* (February and March, Volume 44, Numbers 2 and 3)
1998 – *Sleep-Disordered Breathing* (April and May, Volume 43, Numbers 4 and 5)
1997 – *Consensus Conference IV: Noninvasive Positive Pressure Ventilation* (April, Volume 42, Number 4)
1997 – *Emerging Health Care Delivery Models and Respiratory Care* (January, Volume 42, Number 1)
1996 – *Mechanical Ventilation: Ventilatory Techniques, Pharmacology, and Patient Management Strategies* (April and May, Volume 41, Numbers 4 and 5)
1995 – *Resuscitation in Acute Care Hospitals* (April and May, Volume 40, Numbers 4 and 5)
1995 – *Consensus Conference III: Assessing Innovation on Mechanical Ventilatory Support* (September, Volume 40, Number 9)
1994 – *Controversies in Home Respiratory Care* (April and May, Volume 39, Numbers 4 and 5)
1993 – *Oxygenation in the Critically Ill Patient* (June and July, Volume 38, Numbers 6 and 7)
1992 – *Emergency Respiratory Care* (June and July, Volume 37, Numbers 6 and 7)
1992 – *Consensus Conference II: The Essentials of Mechanical Ventilators* (September, Volume 37, Number 9)
1991 – *Respiratory Care of Infants and Children* (June and July, Volume 36, Numbers 6 and 7)
1991 – *Consensus Conference I: Aerosol Delivery* (September, Volume 36, Number 9)
1990 – *Noninvasive Monitoring in Respiratory Care* (June and July, Volume 35, Numbers 6 and 7)
1989 – *Pulmonary Function Testing* (June and July, Volume 34, Numbers 6 and 7)
1988 – *PEEP* (June and July, Volume 33, Numbers 6 and 7)
1987 – *Mechanical Ventilation* (June and July, Volume 32, Numbers 6 and 7)
1986 – *Neonatal Respiratory Care* (June and July, Volume 31, Numbers 6 and 7)
1985 – *Monitoring of Critically Ill Patients* (June and July, Volume 30, Numbers 6 and 7)
1984 – *Perioperative Respiratory Care* (May and June, Volume 29, Numbers 5 and 6)
1983 – *The Management of Acute Respiratory Failure* (May, Volume 28, Number 5)
1982 – *Complications of Respiratory Therapy* (April, Volume 27, Number 4)

The proceedings published in the February and March 1999 issues are of tremendous importance to respiratory care practitioners everywhere. The "mystery" and future of inhaled nitric oxide are analyzed as never before. We are proud of bringing to you these proceedings and we hope they serve you well in your daily practice. The profession owes a great deal to the many individuals responsible for presenting and publishing the conference proceedings: The Editorial Board, the speakers, the Conference Chairmen, Editor In Chief, Dr. David Pierson, and staff. We also owe much more to INO Therapeutics, Inc. for their generous grant that allowed the gathering of the foremost experts in the practice of inhaled nitric oxide.

Sincerely,

Ray Masferrer RRT
Managing Editor, RESPIRATORY CARE

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Foreword: Inhaled Nitric Oxide: The 1998 RESPIRATORY CARE Journal Conference

Nitric oxide is a fascinating molecule. Our knowledge about nitric oxide traces back to Alfred Nobel, the inventor of dynamite, the active ingredient of which, nitroglycerin, is now used medically as an nitric oxide donor. In 1998, a part of Nobel's legacy, the Nobel prize in Physiology and Medicine, was awarded to Furchgott, Ignarro, and Murad for their discovery of the biologic action of nitric oxide. Therapies arising from our understanding of nitric oxide biology include strategies to potentiate nitric oxide production (such as with the popular drug sildenafil [Viagra]), for inhibiting nitric oxide production (for instance, treatment of sepsis with nitric oxide inhibitors), and for administering nitric oxide (treatment of respiratory failure with inhaled nitric oxide). In contribution to this fertile field of research, RESPIRATORY CARE publishes these special issues on nitric oxide.

The success of any conference is the result of the hard work of its participants, and the attendees at this conference brought together a great deal of expertise, as well as many new research results. This conference may have been the most multidisciplinary Journal conference yet: the presenters included anesthesiologists, pulmonologists, intensivists, neonatologists, and respiratory therapists from the United States, Canada, and Europe. Each of the presenters has made significant contributions to the study of nitric oxide. As their published manuscripts reflect, each presenter approached his topic rigorously and completely. The presentations were expert and the discussions were lively and informative.

When planning this conference, we tried to include discussions of all aspects of inhaled nitric oxide therapy. Included here are discussions of the biologic basis for nitric oxide therapy, its applications in acute and chronic lung diseases of adults and children, the role of nitric oxide in sepsis, the use of nitric oxide in organ transplantation, and as a drug affecting blood elements. The measurement of nitric oxide in exhaled gas and the administration of nitric oxide are carefully discussed.

Although inhaled nitric oxide remains an investigational drug, thousands of patients have received inhaled nitric oxide as part of investigational protocols. When nitric oxide becomes an approved therapy, the readers of RESPIRATORY CARE will be expected to be expert in its safe and proper administration. To this end, we present these issues of RESPIRATORY CARE as a primer for clinicians who need to understand the current status of inhaled nitric oxide therapy.

Dean R Hess PhD RRT FAARC
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The Biology of Nitric Oxide

Margaret Aranda MD and Ronald G Pearl MD PhD

Introduction
Nitric Oxide Production
  Constitutive Nitric Oxide Synthase (cNOS)
  Inducible Nitric Oxide Synthase (iNOS)
  Inhibition of NOS
Mechanism of Action of NO
Non-cGMP-mediated Reactions
NO Donors
NO Adjuncts
The Physiologic Role of NO
  Exhaled NO
  Gender Differences
  Endothelium
  The Heart
  Platelets
  Cancer
  Blood Cells
  The Lung
  Sepsis
  Inflammation and Infection
  Central Nervous System
  Renal
  Skeletal Muscle
  Penis
  Eye
  Gastroenterology
  Stroma-Free Hemoglobin
INO Rebound Phenomenon
Summary

[Respir Care 1999;44(2):156–166] *Key words: nitric oxide, NO, inhaled nitric oxide, nitric oxide synthase, vasodilation.*

Introduction

Endothelium derived relaxing factor (EDRF) was identified in 1980 by Furchgott and Zawadzki,[1] and subsequently identified as nitric oxide (NO). Major discoveries and events related to NO and inhaled nitric oxide (INO) therapy are listed in Table 1. Our current understanding is that NO is a ubiquitous substance that not only plays a major role in vasodilation, but is also implicated in the physiology of all organ systems. Many excellent recent review articles on NO have been published.[2,3,4] This review will emphasize the biology of NO, including its biosynthesis and its biologic roles in health and disease.

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Table 1. Major Events and Discoveries in NO Research

Year	Event or Discovery	Number of Articles Published
1935	Drabkin describes NO interactions with hemoglobin	
1980	EDRF mediates endothelial relaxation	26
1987	EDRF is identified as NO	50
1988	NO used for PPH	59
1992	NO is "Molecule of the Year" in *Science* magazine	682
	NO first used in cardiac surgery	
1993	Frostell first uses NO for ARDS	1178
	Abman first uses INO with HFOV in neonates	
	NO first used for heart transplantation	

ARDS = acute respiratory distress syndrome; EDRF = endothelium-derived relaxing factor; HFOV = high frequency oscillatory ventilation; NO = nitric oxide; INO = inhaled nitric oxide; PPH = primary pulmonary hypertension; Number of Articles = general human and animal studies published in English in the listed year.

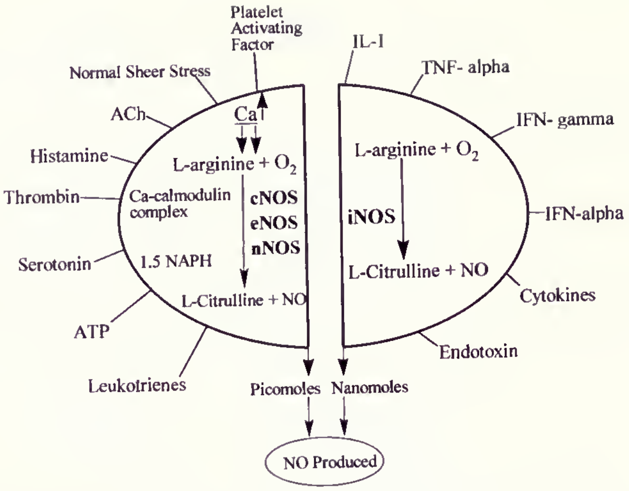

Fig. 1. Endogenous NO production. Through such factors as normal sheer stress or endotoxin, NO is produced from the amino acid L-arginine. Only picomoles of NO are produced under normal conditions, whereas nanomoles of NO are produced from iNOS stimulation under such conditions as sepsis. Ach = acetylcholine; ATP = adenosine triphosphate; cNOS = constitutive nitric oxide synthase; IFN = interferon; IL = interleukin; iNOS = inducible nitric oxide synthase; NO = nitric oxide; nNOS = neuronal nitric oxide synthase; O_2 = oxygen; TNF = tumor necrosis factor.

Nitric Oxide Production

NO is synthesized by an enzyme, nitric oxide synthase (NOS), which combines the amino acid L-arginine with molecular oxygen to produce L-citrulline and NO. There are 3 major isoforms of NOS. Two of these are termed "constitutive" because they are normally expressed in tissues, and the third isoform is termed "inducible" because it is expressed only after enzyme induction has occurred.

Constitutive Nitric Oxide Synthase (cNOS)

The 2 constitutive NOS (cNOS) enzymes were initially designated for the first cell types in which they were found, namely in endothelial (eNOS, or NOS III) and in neuronal cells (nNOS, or NOS I). However, both isoforms are found in many other cell types, including platelets and polymorphonuclear leukocytes. The cNOS isoforms are normally expressed in these cells. After binding of a calcium-calmodulin complex, cNOS is activated and small quantities (picomoles) of NO are produced. eNOS, which mediates endothelium-induced relaxation, is normally active, secondary to sheer stress and factors that stimulate its activity (Fig. 1). Dopamine agonists such as apomorphine enhance NO synthesis.[5]

Inducible Nitric Oxide Synthase (iNOS)

In contrast to cNOS, iNOS (NOS II) is normally not expressed in cells, and its production is stimulated only under certain conditions, such as Gram-negative sepsis (see Fig. 1). Following induction, large quantities (nanomoles) of NO are produced in cardiac myocytes, vascular smooth muscle, fibroblasts, macrophages, and phagocytes, leading to cardiac depression, loss of vascular tone, and macrophage-initiated bacterial lysis. iNOS activation is independent of calcium concentration, and no calcium-calmodulin complex forms. Cytokines that induce iNOS also inhibit nNOS and eNOS expression.[6]

Inhibition of NOS

L-arginine analogs competitively inhibit NO synthesis. Such analogs include N^G-monomethyl-L-arginine, N^G-nitro-L-arginine methyl ester, N^G-nitro-L-arginine, and N^G-amino-L-arginine. These inhibitors are active against all 3 isoforms of NOS. In contrast, at appropriate doses, the cerebral-specific 7-nitroindazole inhibits brain NOS in vivo without blood pressure effects, indicating no inhibition of eNOS.[7] Drugs that decrease NO synthesis include serotonin selective reuptake inhibitors.[5]

Decreased activity of iNOS may occur either through decreased iNOS expression or inhibition of enzyme activity. Inhibitors of iNOS expression include glucocorticoids, interleukin 4, interleukin 10, macrophage deactivating factor, prostaglandin E_2, isoforms of transforming growth factor-β, platelet-derived growth factor, and epidermal growth factor.[8] Since these inhibitors affect enzyme expression only, they are effective only when given prior to stimuli (eg, endotoxin) which initiate iNOS expression. Selective

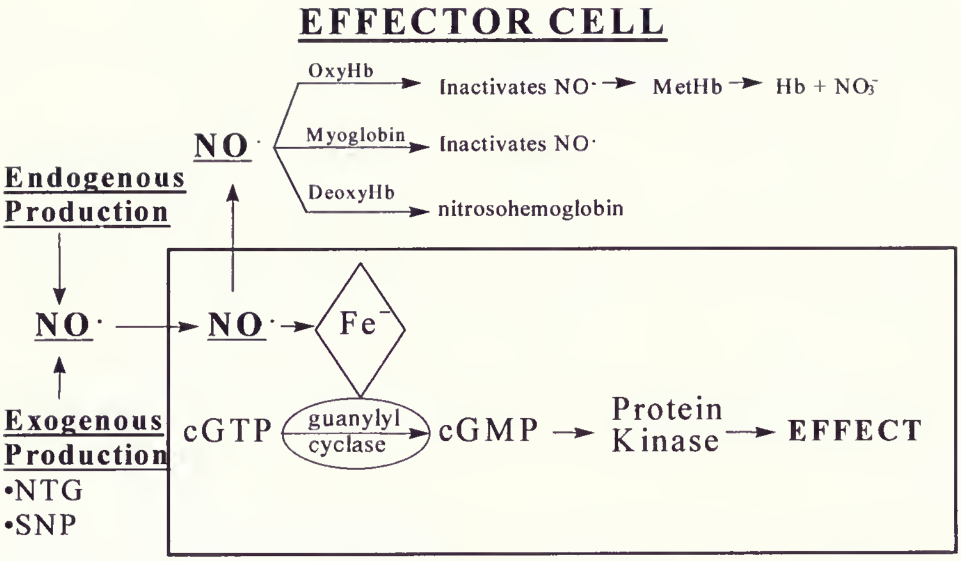

Fig. 2. cGMP-mediated NO interactions in the cell. After NO production, NO diffuses into the effector cell. NO binds to the iron moiety of guanylyl cyclase, and then an increase in cGMP results in a cascade of events which cause an effect (eg, smooth muscle vasodilation). cGMP = cyclic guanidine monophosphate; deoxyHb = deoxyhemoglobin; Fe = iron; cGTP = cyclic guanidine triphosphate; MetHb = methemoglobin; NO = nitric oxide; NO_3^- = nitrate; NTG = nitroglycerin; OxyHb = oxyhemoglobin; SNP = sodium nitroprusside.

inhibitors of iNOS enzyme activity (which are effective after enzyme synthesis) include aminoguanidines, aminoethyl-isothiourea, S-methyl-isothioureas, amides, other isothioureas and guanidine inhibitors.[9] Mercaptoalkyl guanidines act as iNOS inhibitors, or as combined iNOS and cyclooxygenase inhibitors.[10] Mercaptoethylguanidine is a combined inhibitor of both iNOS and peroxynitrite (formed by reaction of NO and superoxide).

Mechanism of Action of NO

The NO molecule is an uncharged free radical with an unpaired electron (NO•). It is lipid soluble and rapidly diffuses across cell membranes to react with other biologic compounds. Most of the physiologic effects of NO result from its binding to the iron moiety of the heme portion of the enzyme guanylyl cyclase. This activates guanylyl cyclase, which then converts cyclic guanidine triphosphate to cyclic guanidine monophosphate (cGMP). Through a series of actions involving protein kinase activation and dephosphorylation of myosin light chains, the net effect (eg, vasodilation) then occurs (Fig. 2). Many of the effects of increased cGMP are due to cGMP-inhibition of cyclic adenosine monophosphate phosphodiesterase (type III phosphodiesterase). NO also reacts with the iron-sulfur centers of many enzymes, resulting in alterations of their activity. The cytotoxic effects of NO involve inhibition of mitochondrial enzymes, decreased aerobic metabolism, inhibition of ribonucleic acid (RNA) replication, and damage to deoxyribonucleic acid (DNA). NO results in activation of cyclooxygenase in macrophages and alterations in second messenger systems and ligand-gated ion channels.

Non-cGMP-mediated Reactions

The half-life of NO varies inversely with its concentration, such that the physiologic half-life can be 0.1–5 seconds or longer.[11] NO is a reactive molecule that combines with many other substances, resulting in multiple possible end-products (Fig. 3). In gas phase, NO combines with oxygen to form nitrogen dioxide (NO_2) in the following reaction:

$$2\,[NO] + [O_2] \rightarrow [NO_2]$$

The NO concentration is disproportionally important in determining NO_2 formation. NO_2 forms when NO is blended with O_2 for delivery to patients. Delivery of higher oxides of nitrogen may lead to pulmonary edema, acid pneumonitis, and death.[12] In water, NO combines with oxygen to produce nitrogen dioxide (NO_2), which then combines with NO to produce nitrite. The half-life of NO in aqueous solutions is inversely related to the oxygen and NO concentrations. However, under physiologic conditions the major pathway for NO metabolism is its combination with superoxide anion (O_2^-), which produces peroxynitrite. Peroxynitrite damages cells by oxidation of DNA bases[13] and reaction with metalloproteins to form toxic nitrosylating species such as nitronium ion (NO_2^+).[14] Peroxynitrite may nitrosylate and thereby activate or inactivate major enzymes. Hemoglobin inactivates NO. Drabkin described interactions of NO and the hemoglobin mole-

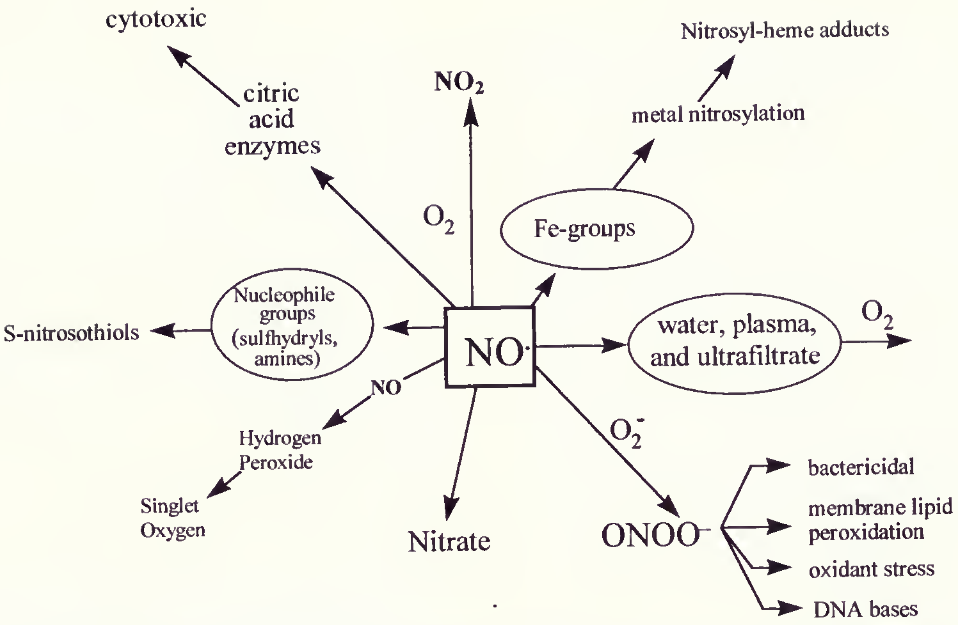

Fig. 3. Non-cGMP-mediated effects of NO. In addition to reactions with the iron group of guanylyl cyclase, NO has biologic reactions with proteins, oxygen, superoxide anion, and with sulfur groups. cGMP = cyclic guanidine monophosphate; Fe = iron; NO = nitric oxide; O_2 = oxygen; O_2^- = superoxide anion; NO_2 = nitrogen dioxide; S = sulfur; $ONOO^-$ = peroxynitrite; N_2 = nitrogen gas.

cule in 1935.[15] NO combines with hemoglobin to form S-nitrosyl-hemoglobin, which subsequently produces methemoglobin and nitrate (NO_3^-). The physiologic half-life of NO will depend upon the concentration of NO, oxygen, superoxide, proteins, and the accessibility to hemoglobin.

NO Donors

Commonly used NO donors include nitroglycerin, sodium nitroprusside (SNP), and hydralazine. Nitroglycerin requires a thiol for nitrosothiol production and releases NO from vascular cells, whereas SNP directly releases NO.[16] Nitrogenated reservoirs of NO include sulfhydryl radicals such as S-nitrosoalbumins and S-nitrosohemoglobins. S-nitrosoglutathione (GSNO) and S-nitroso-N-acetylpenicillamine (SNAP) serve as donors. More recently discovered NO donors include FK409, FR146801,[17] pseudonitroles, and their dimeric azodioxides.[18]

NO Adjuncts

Other intravenous or inhaled agents may provide additional vasodilator effects when used in combination with NO. The effects of NO are additive or synergistic to those of agents that increase cyclic adenosine monophosphate, such as isoproterenol, adenosine, and prostacyclin. Inhaled prostaglandin E_1, a vasodilator extensively cleared by the lungs, may improve oxygenation in patients with acute lung injury.[19] Zaprinast (an inhibitor of type 5 phosphodiesterase, which is specific for cGMP), increases the effects of NO.

The Physiologic Role of NO

After discussing the normal role of endogenous NO, the pathophysiology of altered NO states will be discussed, as well as the use of INO when applicable. Studies examining the role of NO in a specific organ often yield contradictory results because of the multiple cell types present in a single organ, the different NOS isoforms, differences among NOS inhibitors, actions of NO on both local cells and on organ blood flow, and the presence of both physiologic and toxic (eg, peroxynitrite) effects of NO. Related topics include the delivery and monitoring of INO, and the use of INO for acute respiratory distress syndrome, primary pulmonary hypertension, cardiac and lung surgery, and organ transplantation.

Exhaled NO

NO is present in exhaled gas at various concentrations in various species. Lundberg et al[20] reported that in humans paranasal sinus production of NO ranges from 890 parts per billion to 300 parts per million. Single-breath-exhaled NO is a valid measure of tracheal or bronchus NO.[21] Healthy subjects have approximately the same exhaled NO levels as asthmatics treated with inhaled corticosteroids. Lower levels of exhaled NO occur in smokers, and intubated patients may have little or no exhaled NO.[22]

Gender Differences

Estrogen stimulates NO production,[23] and acetylcholine infusion releases more NO in females than in males. In humans, vasodilation caused by estrogen is mediated through NO, possibly mediating cardioprotective effects.[24] During pregnancy, further increases in NO production[25] may maintain quiescence of the uterus.[26] In post-menopausal women, exogenous estradiol therapy results in higher plasma NO levels.[27] Altered NO states occur in women with polycystic ovaries,[28] endometriosis, adenomyosis,[29] and preeclampsia.[30] In the obstetric emergency of retained placenta, nitroglycerin relaxes the uterus.

Endothelium

Furchgott and Zawadzki[1] discovered EDRF as a compound synthesized by endothelial cells and that produces vasodilation of adjacent vascular smooth muscle. EDRF was later identified as NO or a nitrosothiol that resulted in release of NO. The preferential venodilation caused by organic nitrates such as nitroglycerin may be secondary to the relatively lower concentrations of endogenous NO in veins versus arteries.[31]

Deficiency of endothelial eNOS is implicated in causing essential hypertension, although this eNOS deficiency might not occur universally,[32,33] and might actually be a consequence rather than a cause of hypertension.[34] The incidence of essential hypertension and its complications is significantly greater in blacks than in whites. Blacks may have a reduced NO-dependent ability to vasodilate during mental stress,[35] leading to a decreased sensitivity of NO-dependent smooth muscle vasodilation. Decreased eNOS occurs in human atherosclerosis.[36] Knock-out mice which lack the gene for eNOS are hypertensive. Endothelial dysfunction with decreased NO release is present in hypertension, atherosclerosis, diabetes mellitus, and smokers. Increasing NO levels with dietary supplementation with L-arginine, increasing NO release with angiotensin converting enzyme inhibitors, and decreasing NO metabolism with antioxidants all protect against the development of atherosclerosis in laboratory animals.

The Heart

eNOS is present in endocardial and coronary vessel endothelium. Its effects include:

- Coronary metabolic vasodilation
- Mediates coronary vasodilation caused by adenosine
- Cardiac contraction
- Coronary vasodilation after cardiac pacing
- Chronotropy
- Mediates thrombosis and platelet adhesion.

iNOS is implicated in causing the cytokine-induced myocardial depression of septic shock. Perioperative hypomagnesemia may inhibit NO release from the coronary endothelium after cardiac surgery, leading to coronary vasoconstriction and thrombosis.[37]

It is controversial as to whether heart failure causes increased,[38,39] decreased,[40,41] or unchanged[42] NO release from systemic and pulmonary vessels. INO might facilitate cardiac surgery and ventricular assist device placement.

Platelets

In the resting phase, no platelet NO synthesis is detectable. NOS is activated during platelet aggregation.[43] Since platelets contain no DNA and have only residual RNA, proteins are derived from the circulation or by transfer from megakaryocytes.[44] Human megakaryoblastic cells contain cNOS and can express iNOS after being stimulated with interleukin-1-β and tumor necrosis factor-α (TNF-α). Alterations in endogenous platelet NO affect several disease states:

- Arteriosclerosis
- Thrombotic disease
- Tumor metastasis
- Cytokine-induced endotoxic shock
- Uremia
- Diabetes mellitus.

In these diseases, endothelial NO production is inhibited, and platelet dysfunction and platelet-derived growth factor may cause plaque and thrombosis formation. Not only is in vitro platelet aggregation inhibited by NO, NO may also *dis*aggregate formed platelet aggregates.[45]

The anti-anginal effect of isosorbide decreases platelet activity in patients with coronary artery disease.[46] Platelet function may be affected by INO, leading to decreased thrombi.[47] Other NO donors such as SIN-1 and SNP are able to stimulate fibrinolysis.[48]

Cancer

Platelets aggregate with tumor cells, facilitating vascular endothelial adhesion of the complex.[49] Tumor cells with high NOS activity have a decreased ability to form metastases by way of a platelet aggregation mechanism.[50] NO may mediate tumor angiogenesis, and may maintain or increase tumor blood flow.[51] Animal studies show that iNOS upregulation inhibits metastases.[52]

Blood Cells

The red blood cell inactivates NO by forming S-nitrosohemoglobin, which releases its NO group upon deoxygenation, and has anti-platelet effects through a cGMP-independent mechanism. Small vessels may thus maintain anti-platelet function, and erythrocytes may diminish the otherwise proaggregatory results of oxidative stress.[53]

The Lung

Animals show a progression of eNOS expression in the fetal lung during late gestation.[54] Human airway epithelium expresses all 3 NOS isoforms. There are regional differences in eNOS production in the vascular endothelium,[55] and nNOS is present in nonadrenergic, noncholinergic nerves. iNOS also occurs in alveolar macrophages, vascular endothelium, and vascular smooth muscle.[56]

Higenbottam[55] described changes in the muscular pulmonary arteries that distribute pulmonary blood flow and respond to hypoxemia by diverting blood flow from underventilated lung regions. Alterations in pulmonary eNOS may therefore potentiate hypoxic pulmonary vasoconstriction in matching ventilation and perfusion.

In animal models, decreased eNOS expression contributes to hypoxic pulmonary hypertension,[57] congenital diaphragmatic hernia,[58] and pulmonary hypertension due to ductus arteriosis ligation.[59] Hypoxia reduces NO production in vitro, as well as in vivo, leading to decreased exhaled NO concentrations.[55] In animals, NOS inhibition increases baseline pulmonary vascular tone only in certain species, suggesting that the contribution of NO to the low resting pulmonary vascular tone is species-dependent.[55] In all species, NOS inhibition increases the response to pulmonary hypertensive stimuli, suggesting that NO opposes pulmonary hypertension in all species.

Increased exhaled NO can be a means to assess inflammation and the severity of asthma.[60] Patients with acute respiratory distress syndrome have lower concentrations of exhaled NO than other mechanically ventilated patients.[61] Additionally, exhaled NO levels are higher in patients with unstable chronic obstructive pulmonary disease than in patients with chronic obstructive pulmonary disease who are receiving inhaled steroids, or smokers with chronic bronchitis without air flow limitation.[62]

Patients with pulmonary hypertension have a normal basal release of NO.[55] Peak expiratory NO levels are elevated in patients with bronchiectasis,[63] upper respiratory infections, and in asthmatic patients not receiving corticosteroids. Altered NO production occurs in hypoxic lung disease,[64] during heart-lung transplantation,[65] in inflammatory lung disease,[66] and in cystic fibrosis.

Although NOS activity is increased in lung tissue of patients with cystic fibrosis, nasal and exhaled NO are decreased. Sputum NO metabolites correlate with lung function in these patients, suggesting that a smaller amount of airway NO is formed, or that the metabolism or retention of NO occurs in airway secretions.[67]

INO is used in a variety of pulmonary diseases, including acute respiratory distress syndrome, primary pulmonary hypertension, and lung transplantation. No abnormalities were found at follow-up in acute respiratory distress syndrome patients who had received INO.[68]

Sepsis

Endotoxemia and sepsis lead to iNOS stimulation. Only 2 compounds are able, by themselves, to stimulate iNOS: lipopolysaccharide (LPS) and interferon (IFN)-γ. Lipopolysaccharide is particularly important in this process, as it further initiates macrophage-induced TNF-α, IFN-α, and IFN-β production. This stimulates a direct pathway of iNOS stimulation involving IFN regulatory factor 1, tyrosine kinases, and nuclear factor κ B. Other agents, such as cytokines and microbial compounds, act together to induce iNOS.[69]

L-arginine inhibitors blunt the myocardial depressant effects of iNOS, and beneficial effects may include improved perfusion pressure, responsiveness to exogenous catecholamines, and improved cardiac output. Unfortunately, adverse effects include increased systemic vascular resistance, increased pulmonary artery pressure, decreased cardiac output, and platelet accumulation.

L-arginine inhibitors used to date do not change mortality.[70] The nonselective stimulation of both eNOS and iNOS cause adverse effects. In laboratory animals, L-canavanine (an iNOS-selective inhibitor) increases survival. It is unknown whether selective iNOS inhibition will change mortality though, because even iNOS knockout mice have no change in mortality with sepsis.[70]

Inflammation and Infection

NO has both pro-inflammatory and anti-inflammatory roles. Macrophages release NO gas, killing pathogenic microorganisms in the area. NO also increases TNF and interleukin 8 production and activates cyclooxygenase, which results in formation of prostaglandins. NO decreases cytokine production and the oxidants produced by neutrophils.[71]

Central Nervous System

The role of NO in the central nervous system may be protective or cytotoxic, depending on the NO concentration, effects on cerebral blood flow, and on the ratio of NO to prostanoids.[72] Cerebral blood flow is controlled by basal NO release.[73] NO mediates changes in cerebral blood flow in response to altered arterial carbon dioxide tension. NO may act as a cerebellar presynaptic neurotransmitter, aiding Purkinje cells as a "retrograde neurotransmitter," communicating from the postsynaptic neuron to the presynaptic site. This may potentiate memory formation or assist with neuronal plasticity (allowing synapses to attain a new function).[74]

In vitro studies on cultured cortical neurons show that increased NO concentrations cause neuronal death, and NOS inhibition prevents the glutamate-induced neuronal death implicated in stroke.[75] Increased nNOS production occurs during ischemia and stroke,[76] and nNOS inhibition may effectively treat stroke.[74]

Increased basal NO levels may occur with chronic cerebral vascular disease, and dysfunctional endothelial NO synthesis is seen in patients with ischemic attacks and stroke.[77] Human brain tumor biopsies show that eNOS expression decreases away from the tumor, and that glioma and meningioma express all 3 NOS isoforms.[78] In humans, NO may therefore be produced in tumor cells and surrounding vessels, contributing to peritumoral edema.

Increased oxidative damage from peroxynitrite formed from NO and superoxide anion is implicated in sporadic and familial amyotrophic lateral sclerosis (ALS),[79] and in other neurodegenerative disorders, such as Huntington's disease and Alzheimer's disease.[80] Animal studies show that hyperoxia-induced seizures are NO-mediated.[81]

NO increases the minimum alveolar concentration for general anesthetics. Halothane and isoflurane inhibit endothelial eNOS, but not iNOS.[82] NOS inhibition decreases minimum alveolar concentration for halothane. The nNOS-specific inhibitor 7-nitroindazole decreases minimum alveolar concentration without causing systemic hypotension.[83]

NO modulates opiate effects and pain, with intravenous opiates leading to NO production.[84] After prolonged noxious stimuli, spinal NO results in hyperalgesia and allodynia. Spinal nNOS is activated by cholinergic stimulation, causing antinociception.[85] NOS inhibition prevents spinal sensitization after formalin injection in the rat.[86]

Renal

Endogenous NOS assists in human adaptation to increased dietary sodium, affecting renal glomerular filtration rate, plasma flow, sodium excretion, systemic hemodynamics, and renin secretion.[87] NO may also modulate renal perfusion pressure and sodium excretion by transmitting the renal pressure into the interstitium.[88] NO inhibition with N^G-monomethyl-L-arginine causes renal vasoconstriction, decreases GFR, and increases filtration fraction and sodium reabsorption. An increase in endogenous NO has been implicated in causing hypotension during hemodialysis.[89]

Skeletal Muscle

The sarcolemma of muscle fibers is associated with nNOS, and eNOS occurs in mitochondria. Basal NO release in isolated skeletal muscle occurs at a low rate; during exercise, production increases. Actions of NO include vasodilation and altered muscle metabolism, involving mitochondrial oxygen consumption and creatine kinase activity. NO inhibits the force of contraction through alterations in excitation-contraction.[90] In patients with crush syndrome, increased NO or decreased NO excretion occur.[91] In patients with multiple sclerosis, increased NO metabolites (nitrate and nitrite) occur in cerebrospinal fluid and serum.[92]

Penis

Erection is caused by cNOS production from nonadrenergic noncholinergic nerve terminals, penile blood vessel endothelium, and the smooth muscle of the corpus cavernosus. Sildenafil, which inhibits cGMP-specific phosphodiesterase-5, potentiates NO production, leading to cavernosal smooth muscle relaxation during sexual stimulation.[93] With aging, erectile dysfunction occurs. Animal studies indicate that eNOS upregulation and altered calcium concentrations occur.[94] In isolated human corporeal muscle strips, digoxin-induced erectile dysfunction may be secondary to sodium pump dysfunction leading to contraction, therefore precluding NO-induced relaxation. As such, digoxin may treat recurrent priapism.[95]

Eye

In vitro, nitric oxide depresses retinal gamma-aminobutyric acid receptor function.[96] In diabetes, eNOS expression is inhibited in retinal endothelial cells in vitro.[97]

Gastroenterology

NO regulates esophageal motility and modulates the hepatic and mesenteric circulations. The timing of post-swallowing esophageal propulsion is NO-dependent, affecting the latency period between the swallow and muscle contraction. Diffuse esophageal spasm may be relieved with the use of the NO donor nitroglycerin.[98]

cNOS production is increased in cirrhotic ascites,[99] and has been implicated in impairing arterial oxygenation[100] in those patients. In cirrhotic patients given L-arginine infusion, the hepatic and mesenteric vessels are preferentially vasodilated, suggesting increased NO production in these areas.[101] Elevated NO levels in ascites occur in cirrhotic patients with severe liver dysfunction, and may predict mortality.[102]

Animal studies show that NO mediates acetaminophen-induced hepatotoxicity[103] and that iNOS may be responsible for inflammatory cascades that later result in acute organ damage to the intestine and liver in hemorrhagic shock.[104] Hypoxemia can be alleviated with the use of INO for congenital diaphragmatic hernia, or hepatopulmonary syndrome.[105]

Stroma-Free Hemoglobin

The development of stroma-free hemoglobin solutions as an alternative to blood transfusion has been limited by inactivation of endogenous NO by its binding to hemoglobin. Adverse effects include increased blood pressure and pulmonary hypertension with increased systemic and pulmonary vascular resistance.[106] Polymerization of the hemoglobin molecules may limit the effects by decreasing the penetration of the hemoglobin into tissues. In animal studies, α-diaspirin crosslinked hemoglobin decreases ischemic brain injury, possibly by binding NO.[107] Low doses of stroma-free hemoglobin can improve blood pressure in endotoxic shock.

INO Rebound Phenomenon

Acute withdrawal of INO may lead to profound hypoxemia, acute pulmonary hypertension, and hemodynamic instability.[108,109] The etiology of this syndrome may include downregulation of endogenous NO production,[110] decreased NO sensitivity,[111] or increased endothelin-1. Prevention and reversal of hypoxia-induced pulmonary hypertension has been shown to occur with endothelin$_A$-selective antagonists.[112]

Summary

Endogenous NO directly or indirectly mediates many primary physiologic functions. NO is a double-edged sword, sometimes serving to help, and sometimes causing harm. NO has both physiologic and toxic effects, and is produced by and acts upon multiple cell types in each organ system. A more complete understanding of the complex effects of NO in health and disease is required for the development of effective therapies.

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Discussion

Rich: That was a great talk and I enjoyed that a lot. You talked a little bit about inactivation of INO, and you also talked quite a bit about systemic effects of endogenous NO. I'm just curious; other than maybe effects on neutrophils and platelets, what are your thoughts about systemic effects of INO, or are there any significant effects?

Pearl: I think we probably have experts here using it, and, certainly, people are now talking about it. Some of the systemic effects being discussed are related to NO having effects on cells as they pass through the lung. The platelets and the neutrophils, as they pass through, will pick up NO, and thus NO increases cyclic GMP in those cells. Even if they don't have NO once they leave the lung, they may have their physiology altered. Alternatively, INO may produce systemic effects by binding to hemoglobin, being carried to the periphery, and released at the periphery. Effects that people have seen include anti-atherogenic effects in patients after carotid angioplasty, decreased myocardial ischemia, and effects on sickle cells, and these have all been well described. We know that INO can affect renal blood flow and platelet function, and prolong bleeding time. I think there are people in the audience who want to comment on systemic effects of INO since Boston is a major place for this.

Head: I think we're still trying to figure out Dr Stamler's work, published in *Nature,*[1] on whether NO is carried on the hemoglobin at the beta cys-93 protein site, or whether it's carried by the heme. I noticed in the slide, which is the way we typically think about NO, as producing nitrosyl-hemoglobin and then methemoglobin. In fact, that may not be the case. NO can directly oxidize the heme and immediately form methemoglobin. It's thought that in the de-oxy state, NO is carried on the beta cys-93 site. This is early work and so there's a lot we don't know. However, I believe, based on our work, that hemoglobin is truly carrying NO to distant sites.[2] Interestingly, there's an abnormal hemoglobin called hemoglobin H, which has 4 beta subunits, as opposed to 2 alpha and 2 beta, and all of those patients have hypertension. As it turns out, NO stays extremely tightly bound to that type of hemoglobin, so the suggestion is that because it can't release NO in the microvasculature, this may be the etiology of their hypertension.[3] So, a lot of work that needs to be done.

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Stewart: I enjoyed your talk. It's amazing to see how complex the biology of NO is. In fact, this complexity is somewhat worrisome. At times it seems to me that we've rushed to the bedside with things that affect the biology of NO, and we really don't know enough about NO. Clinicians have tried INO and we're getting into NO blockers, possibly before we really understand them. What are your comments?

Pearl: I think I agree with you that ideally what one would do is to develop much more basic knowledge, then slowly move to animal studies and refine your basic knowledge of how NO affects things before you ever would get to talking about treatment of clinical problems. But I don't think that's the way science and medicine is really done nowadays. There's a great rush to try to translate some of the new understanding into clinical care. At Stanford, we have cardiologists who are taking arginine religiously, because they are very convinced that it will decrease arteriosclerosis and improve the long-term life expectancy. I don't think we really understand enough to be able to start doing those things. Similarly, I think as we're now re-evaluating INO for ARDS, we're again beginning to recognize how complex the situation is. The initial rush of enthusiasm to try to use NO manipulations therapeutically almost undoubtedly is going to have some major setbacks, because we're taking too simplistic an approach. My hope is that we won't abandon it; instead, what we'll do is go back and find more selective ways of applying NO. I think in particular what we'll need to do is to find out more about the individual situation and have better patient stratification for its use.

Stewart: I echo your concern, especially with INO. I can't tell you how many people are saying to me now "See, it doesn't work," before we really understand who to give it to, how much to give, and what are the complications. Another example is Viagra. It has been rushed to the market, and now we're starting to see that some people are dying on Viagra!

Gerlach: Coming back to the systemic effects of NO, it's even discussed that the pulmonary effects of INO are systemic, because there are some papers showing that if you inhale NO and the vascular resistance is going down, it cannot be on the level where it's inhaled, because the vessels of the alveoli do not contain any smooth muscles.[1] It has been shown that the main effect of lowering the vascular resistance is on the pre-alveolar area, which means that it must have gone at least one circle.[1] Furthermore, the pulmonary smooth muscle cells are very, very sensitive to NO, much more than the systemic ones, and this might be the reason why you see a pulmonary effect if you inhale NO, and not that you inhale it locally in the lung.

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Pearl: I'm not sure I completely agree with that. NO is highly diffusable, and it is able to diffuse through the cells to get to the precapillary arteriolar vessels. And so, in perfused lungs, where presumably we're not seeing any carriage of NO, you'll see the same vasodilator effect. So, it need not necessarily have gone from the alveoli all the way around back to the pulmonary arterioles, as opposed to moving directly through the cells up to the pulmonary arterioles. In the same way, if you think about the effects of hypoxic pulmonary vasoconstriction, you recognize that the alveolar gas is able to affect the pulmonary arteriolar bed.

Gerlach: On the other hand, you probably know the paper of Jonathan Stamler's group,[1] which showed that if, for instance, the oxygen gradient between peripheral and pulmonary sections is erased by taking hyperbaric oxygen ventilation, you see absurd effects. You suddenly have vasoconstriction, because the NO is not delivered in the periphery anymore. And so probably the NO that you inhale might be autoinhaled endogenous NO, which definitely has a function in the periphery.

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Pearl: Yes. I think that we've all agreed in terms of the systemic effects that we'll get from it, and I think there is a lot of interest in using those systemic effects therapeutically nowadays. What's impressive, though, is that we really get minimal systemic vasodilation from INO, so that even though there likely is delivery of NO to the periphery, it is not achieving an adequate concentration, at least in the majority of the systemic vasculature.

Hurford: Ron, with the knowledge that there is perhaps a delivered pool of NO and effects on other elements, when you go back and read between the lines in a lot of the literature or just look at the graphs, you see biphasic effects of NO, dependent upon dose. We've always been scratching our heads and trying to explain that. I remember one such study[1] was the effect of INO on coronary restenosis, where at low concentrations, we got good inhibition of platelet aggregation, but at high concentrations, it was very difficult to convince ourselves at all that it was an NO effect, per se. And the same thing, perhaps, for some of the NO studies, where there are different low doses versus high-dose effects.[2] Do you think that represents changes in the delivered pool, or how do you explain away those findings? Random variation?

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Pearl: Since you've spent much more time, I probably should ask you how to explain them. But one thing, obviously, about low- versus high-dose is always going to come back to the peroxynitrite issue and whether, when you're starting to see loss of beneficial effects at higher doses that's related to peroxynitrite formation, where most of the effects you'd expect would be the reverse of those of NO. The other explanation would involve systemic effects. As the NO concentration increases, are we starting to activate other enzymes, or are we beginning to get other cell types involved? All become real issues, and when you're applying this to something like coronary restenosis, where we don't remotely understand the physiology, it becomes very difficult to answer. What were your thoughts, since you did think about it?

Hurford: That's why I asked the question. I was hoping you could help me out. I think that perhaps what you've talked about, the balance between the "evil" effects, if you will, the peroxynitrite effects and the toxic effects of NO, is a dose-response. I also wonder whether, at least for INO, we just end up delivering more to the periphery, and it becomes more biologically active with dose. So, those effects are showing up as a more dose-responsive effect. So I wonder whether it's a general versus a peripheral effect of NO, on a simplistic basis, at least when applied to the lung.

Pearl: One interesting thing to me is that, if you look at some specific effects, we really do reach a maximum effect at fairly low NO concentrations. And one would believe that, as we continue to increase, we're going to stop seeing that effect, beneficial or harmful, and start to see second effects, which, presumably, explain what's occurring.

Inhaled Nitric Oxide for Hypoxemic Respiratory Failure of the Newborn

Jesse D Roberts Jr MD

Introduction
Inhaled Nitric Oxide and Persistent Pulmonary Hypertension of the Newborn
Non-Response to INO
Neomuscularization and Remodeling
Safety of INO
Summary

[Respir Care 1999;44(2):169–173] *Key words: nitric oxide, NO, inhaled nitric oxide, pediatrics, neonatology, acute respiratory distress syndrome, ARDS, persistent pulmonary hypertension, pulmonary, acute respiratory failure, adverse effects.*

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is associated with decreased pulmonary blood flow and shunting of deoxygenated blood from right to left across the ductus arteriosus and foramen ovale. This extrapulmonary shunt of blood causes severe systemic hypoxemia that is not ameliorated by breathing high levels of oxygen.[1] Although the etiology of PPHN is unknown, 2 mechanisms cause decreased pulmonary blood flow in PPHN.[2] First, the pulmonary arteries have increased tone and abnormal responsiveness to vasodilators. Second, the pulmonary arteries in the lung periphery are precociously muscularized,[3] causing a decrease in vascular cross sectional area. The latter mechanism restricts blood flow and causes pulmonary hypertension that is not decreased by vasodilators.[4]

Current therapies for PPHN include ventilation with high levels of oxygen, induction of alkalosis, and the use of intravenous vasodilators (see review by Roberts and Shaul[5]). Although intravenous vasodilator drugs such as tolazoline decrease pulmonary vasoconstriction in some patients, they do not selectively dilate pulmonary arteries, and they often cause systemic hypotension. In addition, intravenous vasodilator drugs may vasodilate nonventilated lung segments and thereby increase intrapulmonary shunting of blood. If these therapies fail, extracorporeal membrane oxygenation (ECMO) can be life-saving for patients with severe PPHN.

Inhaled Nitric Oxide and Persistent Pulmonary Hypertension of the Newborn

Inhaled nitric oxide (INO) is a potent and selective pulmonary vasodilator in the newborn. In addition, INO has been observed to decrease the pulmonary vasoconstriction in PPHN, and to increase arterial oxygen tension (P_{aO_2}). Recent laboratory studies suggest that INO prevents pulmonary artery remodeling that causes pulmonary hypertension in newborn offspring.

INO is a selective pulmonary vasodilator. Frostell et al[6] found that INO at 40–80 parts per million (ppm) by volume completely reverses pulmonary vasoconstriction in awake, spontaneously-breathing sheep. INO has also been observed to be a potent and selective pulmonary vasodilator in the newborn. In anesthetized and ventilated newborn lambs, breathing 10% oxygen (fraction of inspired oxygen [F_{IO_2}] set at 0.10) causes pulmonary vasoconstriction, whereas breathing 20–80 ppm INO at F_{IO_2} 0.10 was observed to rapidly reverse the pulmonary vasoconstriction.[7] The maximum decrease in hypoxic pulmonary vasoconstriction in the newborn lambs occurred while they

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received 80 ppm INO, and increasing the INO concentration to 160 ppm did not cause systemic vasodilatation. INO causes pulmonary vasodilation by stimulating guanylate cyclase, which increases lung cyclic guanidine monophosphate (cGMP),[7] which is a second messenger of nitric oxide (NO) in smooth muscle cells. Furthermore, severe respiratory acidosis, caused by ventilating the lambs with 8% CO_2, did not attenuate the pulmonary vasodilation effect of breathing 80 ppm INO. In newborn lambs with PPHN caused by premature constriction of the ductus arteriosus, receiving up to 100 ppm INO causes a rapid, selective, dose-dependent vasodilation of the pulmonary arteries and improves P_{aO_2}.[8] In comparison with mechanical ventilation with high levels of oxygen, treatment with INO improved the survival of lambs with severe PPHN.[9] Studies also indicate that INO dilates the pulmonary vasculature of piglets with sepsis[10] and meconium aspiration.[11] Additionally, INO combined with exogenous surfactant therapy[12] or partial liquid ventilation[13] decreases the pulmonary vasoconstriction and systemic hypoxemia of lambs with pulmonary hypertension and congenital diaphragmatic hernia.

Since INO distributes in highly ventilated alveoli, it may improve the matching of ventilation and perfusion. Studies in adult sheep suggest that INO decreases shunt in animals with lung injury.[14] In a recent study, INO was observed to decrease intrapulmonary shunt and dead space in newborn rabbits with lung injury induced by saline lavage or meconium treatment.[15] It is unknown whether INO decreases intrapulmonary shunt in human newborns with meconium aspiration or pneumonia.

INO increases P_{aO_2} in newborns with PPHN. Pilot studies tested whether INO increases P_{aO_2} in patients with PPHN without causing hypotension. Administration of up to 80 ppm INO was observed to increase the postductal oxygen levels in nearly 70% of patients with severe hypoxemia and PPHN.[16] None of the patients breathing 80 ppm INO developed systemic hypotension or significantly increased methemoglobin concentrations. In addition, in one patient, breathing low levels of INO for 23 days did not cause tachyphylaxis to INO. Although the optimal initial INO level is unknown, other researchers have also observed that breathing lower levels of INO improves P_{aO_2} in infants with PPHN,[17,18] and could lead to a sustained improvement in oxygenation after the INO was discontinued.[17]

In patients with PPHN, INO increases P_{aO_2} in comparison with conventional ventilator therapy with oxygen.[19] In a multi-center study, INO was observed to increase P_{aO_2} in 53% of infants with severe PPHN, whereas control ventilator therapy increased it in only 7%. Importantly, the magnitude of the increase in oxygen levels was directly proportional to the degree of hypoxia before administering INO. With chronic INO, the increased P_{aO_2} was maintained in 75% of the patients. In another multi-center study, the optimal INO level was tested.[20] Although the maximum increase in P_{aO_2} was observed at 80 ppm INO, as little as 5–20 ppm INO increased the oxygen levels above those observed in the hypoxic newborns not receiving INO. Studies suggest that ventilator strategies that increase lung volume, such as high frequency oscillatory ventilation (HFOV), may potentiate the pulmonary vasodilatation caused by INO.[21]

INO decreases the requirement for ECMO in newborns. Although ECMO is life-saving for many infants with severe hypoxemia, it is expensive, requires the availability of a specially trained team, and is not available in many areas. In addition, because ECMO requires systemic heparinization, it can cause intraventricular hemorrhage. In a large multi-center study,[22] INO was observed to decrease the need for ECMO in full-term and nearly full-term infants. In a multi-center study of full-term infants with PPHN, the requirement for ECMO was 71% in full-term infants with PPHN.[19] By contrast, in patients treated with INO the requirement for ECMO therapy was 40%. Because INO decreases the need for ECMO, it is likely, though unproven, that INO diminishes the morbidity of patients with PPHN.

Non-Response to INO

Several mechanisms may prevent INO from increasing oxygen levels in PPHN. Nearly 50% of patients with PPHN do not have an increase in P_{aO_2} when treated with INO.[19] Since PPHN is associated with restriction of blood flow through peripheral pulmonary arteries with thickened walls, it is likely that INO does not increase lung blood flow and P_{aO_2} in those patients. In addition, down-regulation of NO-cGMP signaling pathways in pulmonary arteries may limit the clinical utility of INO. Several animal studies suggest that pulmonary hypertension decreases the activity of soluble guanylate cyclase, an important receptor of NO in smooth muscle cells. In chronically hypoxic rats[23] and lambs with PPHN,[24,25] soluble guanylate cyclase activity and NO-mediated pulmonary artery relaxation are decreased. Studies suggest that treatment with phosphodiesterase inhibitors, which decrease cGMP metabolism, increase the potency of INO.[22,26,27] In one patient, dipyridamole, a phosphodiesterase inhibitor, was observed to potentiate the increase in P_{aO_2} associated with INO.[28] INO might not be effective if delivery or distribution of the gas to the pulmonary vasculature is impaired. In patients with interstitial disease associated with meconium aspiration, the response to INO is often impaired.[22] The use of ventilatory techniques that recruit distal airways, such as HFOV, has been observed to improve P_{aO_2} in newborns receiving INO.[29] Moreover, animal studies suggest that exogenous surfactant or partial liquid ventilation improves the vasodilatation caused by INO in lambs with congenital diaphragmatic hernia.[12,13] It is unknown whether these adjuvants will improve the poor response to INO often observed in patients with lung hypoplasia.[12,30]

Neomuscularization and Remodeling

INO attenuates pulmonary vascular disease in the newborn lung. In the young, lung injury and/or increased pulmonary blood flow causes muscularization of peripheral pulmonary arteries (neomuscularization).[31] The neomuscularization of peripheral lung arteries causes pulmonary hypertension and right heart failure by restricting pulmonary blood flow and increasing pulmonary artery tone. Laboratory studies indicate that chronic INO prevents pulmonary artery neomuscularization in hypoxic animals. In rat pups, chronic hypoxia causes neomuscularization of the peripheral pulmonary arteries, right ventricular hypertrophy, and pulmonary artery hypertension similar to that observed in infants and children with various forms of congenital heart disease.[32–34]

Studies in adult[35] and infant rats[36] demonstrate that chronic INO at 20 ppm attenuates pulmonary vascular remodeling and right ventricular hypertrophy. The mechanism by which chronic INO prevents pulmonary artery remodeling is unknown. Although in vitro studies suggest that NO decreases remodeling by moderating growth factor expression[37] and smooth muscle cell proliferation[38,39] in the animal studies described above, NO probably prevented remodeling by decreasing hypoxic pulmonary vasoconstriction.

It is possible that NO inhibits remodeling by a mechanism that does not require vasodilation. In rat pups treated with monocrotaline (the metabolites of which cause endothelial injury and leakage of growth factors into the media of pulmonary arteries), lung artery neomuscularization occurs before pulmonary hypertension[40] or right ventricular hypertrophy.[41] In a recent study, continuous INO was observed to prevent increased pulmonary artery muscularization, proliferation of cells in the pulmonary artery wall, and cell loss in monocrotaline-treated rat pups before they developed lung artery hypertension.[40] This protective effect observed in rat pups appears to be inconsistent in adult rats. Although 20 ppm INO attenuated pulmonary artery remodeling of peripheral pulmonary arteries of monocrotaline-treated rats, it did not prevent pulmonary hypertension or right ventricular hypertrophy.[42,43] However, treatment with L-arginine (a precursor of endogenous NO)[44] or a phosphodiesterase inhibitor (which increases NO-cGMP signaling),[45] was observed to attenuate monocrotaline-induced pulmonary artery remodeling in adult rats. Together, these studies suggest that INO might have a protective effect against pulmonary artery disease, independent of its vasodilatory effect. Further studies are needed to determine whether INO protects the lung from pulmonary artery remodeling associated with other forms of lung injury.

Safety of INO

Preliminary studies suggest that low concentrations of INO are safe in the newborn lung. In the treatment of newborns with PPHN, carefully controlled quantities of NO are introduced into the inspiratory limb of a constant flow, pressure-limited, time-cycled ventilator or high frequency oscillator breathing circuit. By limiting the concentration of NO introduced into the circuit and the co-residence time of NO and oxygen, the INO level can be controlled and the levels of oxidative gas products of NO (NO_X) can be minimized. Without these precautions, the patient might inhale high levels of NO and NO_X, which can cause pulmonary edema, injury, and death.[46]

In infants receiving ≤ 20 ppm NO for up to 4 days, there was no substantial change in surface activity or in the tracheal aspirate concentrations of the lipid peroxidation products or cytokines (interleukin 1 [IL-1], granulocyte-macrophage colony-stimulating factor, IL-1 receptor antagonist).[47] In addition, other studies report that the duration of ventilator and hospital support was not increased by administration of INO. A comparison of babies receiving up to 80 ppm INO and babies treated with ECMO and not INO, found no difference in the duration of intubation, oxygen therapy, or hospitalization.[19] As well, in full-term and nearly full-term babies with hypoxemia, the duration of oxygen, ventilator therapy, and hospitalization was not significantly different in babies treated with INO and those who did not receive INO.[20]

Other investigations also suggest that INO protects the newborn from injury and remodeling. In ventilated premature lambs with severe respiratory distress syndrome, INO increases pulmonary blood flow without worsening pulmonary edema, and decreases lung neutrophil accumulation.[48] Continuous INO has been observed to inhibit pulmonary artery remodeling associated with lung injury.[40] These results suggest that low levels of INO are not injurious to the newborn lung, and may even be protective.

Although INO primarily works in the lung, it might also stimulate the guanylate cyclase of platelets, which transit through the lung and affect bleeding times. However, the importance of the effect of INO on platelet function is unknown. In newborns treated for PPHN, bleeding time was prolonged by INO,[49] but the in vitro aggregation of platelets obtained from these patients was not changed by INO. In existing research, administration of INO has not been observed to increase the incidence of pulmonary hemorrhage in newborns.

Several studies need to be performed to fully define the safety of INO for newborns. Although an important follow-up study of newborns with PPHN treated with INO has been reported,[50] the comparative outcomes of babies treated with INO, conventional therapy, or ECMO have not been reported. Since INO has been shown to affect cell proliferation and pulmonary artery muscularization, additional study of the effect of INO on postnatal lung development is needed. Such investigation is necessary prior to widespread and prolonged clinical use of INO.

Summary

Current studies indicate that INO is a useful, selective pulmonary vasodilator in newborns and infants with pulmonary hypertension. Laboratory studies suggest that chronic INO inhibits pulmonary vascular remodeling disease associated with chronic pulmonary hypertension or lung injury. Research is currently underway to find ways to augment or potentiate the effects of low levels of INO in the perinatal lung.

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Discussion

Hess: Jay, could you say a few words about an approach to dosing of INO in the newborn?

Roberts: Many of the initial dosing studies used newborn animal models to test the effects of INO in decreasing pulmonary vascular resistance. The clinical studies have been focusing on more clinically relevant variables such as the effects of INO on postductal P_{aO_2} levels. One of the reasons why the Massachusetts General Hospital study started out by using 80 ppm is because we wanted to be certain to get an effect on oxygenation so that we could reach significance in our study. We reasoned that this level of INO would cause more babies to achieve a successful increase in oxygenation. However, as INO is now becoming more of a mature therapy in neonatology, the expectations of successful NO response have changed. Now people are accepting lower increases in postductal P_{aO_2} as evidence that INO is effective. So, as a result of this, lower levels of INO, often less than 20 ppm, are used. If 20 ppm is not effective, some clinicians will increase the INO level up to 80 ppm to see whether oxygenation can be increased. Then, once they demonstrate that INO has been effective, the INO level can be decreased within a few hours, to levels of 20 ppm or lower.

Hess: A follow-up question. What about weaning from a clinical, practical standpoint in the neonatal ICU? When do you wean? How do you wean?

Roberts: That's something that's changing now. Until recently neonatologists have decreased the level of the experimental therapy, which is INO; but I think as time goes on and as clinicians appreciate more how INO safely decreases pulmonary vasoconstriction and increases systemic oxygen levels, they are tending not to wean the INO level. They are now decreasing the inhaled oxygen levels. Decreasing the inhaled oxygen levels in babies who did not respond to the high oxygen levels makes sense since the babies are exhibiting shunt physiology, and oxygen is a toxic gas at high levels. So, now I think what people are starting to do is keep the INO at < 20 ppm, and decreasing the inhaled oxygen levels. Once the F_{IO_2} is significantly decreased, then it might be prudent to decrease the INO. I think what's important about this approach to weaning oxygen therapy is that it will uncover a beneficial effect of INO on lung toxicity.

Stewart: If I was to be convinced that I need to use NO in neonates, and thank the Lord I don't take care of neonates, I would have to be sure that ECMO truly was bad, and I would have to be convinced that your control arm strategies were the best conventional strategies available. In adults, clearly there's a big debate whether prone ventilation or NO or HFO or recruitment maneuvers or permissive hypercapnia are equal to using NO. Could you give me your thoughts on how bad ECMO is, how available is it to clinicians out there, and whether there other things in the conventional arm that could equally prevent ECMO?

Roberts: Well, ECMO is clearly life saving, but it's very expensive, time-consuming, and requires a lot of expertise. As a result of that, it's not available in a lot of medical centers. Not all Level III nurseries in the United States are able to provide ECMO for critically ill babies. Therefore, many very sick babies are transported to other centers for consideration for ECMO therapy. The adverse effects of ECMO primarily seem related to the heparinization required for blood to be circulated through the membrane. That can permit severe bleeding in the brain and other organs. Now, as far as other therapies . . .

Stewart: Just back on that thought, I would have thought that these long-term follow-up studies would have demonstrated that your fears of ECMO were valid.

Roberts: Right. And I would, too, providing one could do an experiment where one could be randomized to NO alone and not use a rescue therapy such as ECMO to back them up. That's the difficulty with the neonatal studies, and will always be a problem as long as ECMO is in the rescue limb. So, you don't always end up with a very clean control group. This is probably why the death rates weren't different in the INO and control groups. So one needs to look at surrogate end points, and right now the surrogate end point that most people are looking at is acute increase in systemic oxygen levels and the requirement for ECMO. It's not that we're saying ECMO is terrible, it's just that there can be important adverse effects and availability issues associated with it.

Stewart: But there were other opportunities in the conventional arm. My second part of the question was HFOV, recruitment maneuvers, prone position.

Roberts: Recruitment maneuvers, which include HFOV, are important and in some studies were included in the conventional arm. The Denver study[1] randomized hypoxic patients who came in with conventional ventilation to ventilation with HFOV alone or conventional ventilation with INO, and for those who failed, they would get crossed-over, so they could examine the effects of lung recruitment by the HFOV maneuver itself, or in combination with INO or systemic oxygen levels. It seems that when we compare HFOV to conventional ventilation with NO, there's about the same increase in postductal P_{aO_2}. But, nevertheless, there are a number of babies who do not improve with HFOV therapy alone. Some of those babies did have increased oxygen levels with combined treatments of HFOV and NO. Several therapies are being tested in newborns with PPHN. However, many of them don't treat the underlying pathophysiology of this disease. For example, HFOV can cause lung recruitment, and prone ventilation may affect the V/Q matching. However, none of them directly relieve pulmonary vasoconstriction. So, they may be useful as adjunctive therapies for babies with interstitial lung disease and PPHN, but INO is a more specific therapy for vasoconstriction.

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Channick: I'm not that familiar with neonates, but just to make it more practical and kind of push you a little bit, you're going to have, presumably, an approved drug in the near future, and you'll be, as a neonatologist, a pioneer in determining how this is used in the community, and in terms of setting protocol and policy. I've heard a counter-argument that having NO in a community setting may actually delay appropriate transfers to large centers, because "any" physician can try it. What are you going to recommend to the community physicians? When should they start it? When should they decide it's not working?

Roberts: That's an important thing, and you are pushing me. The problem with it right now is that INO is still experimental.

Channick: Not for long.

Roberts: Right. It's still experimental, and I think it should be restricted at this point to places where they have the alternative therapies, such as ECMO, readily available. Once INO is approved by the FDA, its application should be limited by neonatologists or intensivists who are familiar with its application. One of the positive things about INO is how rapidly it causes increases in systemic oxygen levels. So, it is possible that a short trial of INO can be used in a Level III nursery where they could determine very rapidly, within a half hour, whether it's effective in a given patient. If it is not effective, ECMO, or transport for ECMO, could be instituted. What's happening, unfortunately, is that a lot of therapies, including INO, high frequency ventilation, exogenous surfactant, prone ventilation, and partial liquid ventilation perhaps down the road, are being tried at centers without ECMO available. If one hour is devoted to unsuccessful use of each one of these therapies, then the baby could worsen over a long period of time, and then be transported in extremis. So, I think that NO, like any other therapy that's going to be used without ready availability of ECMO, should be used cautiously and evaluated very carefully.

Head: One of the things we always worry about with NO toxicity is methemoglobinemia. In your study, you used 80 ppm and a high F_{IO_2}, which certainly enhances the chance of forming methemoglobinemia. However, if I remember correctly, you didn't see much methemoglobin formation in these babies. Is that correct? And in the ones who did have methemoglobinemia, how do you recommend treating those patients?

Roberts: In our trial, we used 80 ppm INO initially, and then rapidly decreased. Although the methemoglobin increases in proportion to the INO concentration and duration, breathing 80 ppm for short periods of time brings the methemoglobin level up only to the 5–8% percent range. In one case, however, which we've discussed in our multi-center study, there was a methemoglobin level that went up to nearly 15%. Despite this level of methemoglobin, there was no evidence of metabolic acidosis or other effects of decreased oxygen delivery. The treatment for high methemoglobin includes decreasing the INO level, which was, obviously, done, and treatment with vitamin C.

Pearl: In the adult population with acute respiratory distress syndrome, rebound from NO therapy is a substantial problem. Is it also a problem in neonates? Do you have any suggestions for strategies for it?

Roberts: It is a problem in newborns. In babies, much like in adults, there is a 5–10 minute period of unstable postductal oxygen levels, or saturations, associated with acutely decreasing INO levels. A typical way that people treat that is by increasing the NO. However, one could ratchet up the NO level to as high as you can go if you use this approach. Another approach is to realize that the instability in the postductal oxygen saturation will last only about 15 minutes, and that one can either ride through it, accept the saturation drop, or just transiently increasing the F_{IO_2}, prior to decreasing NO, to keep the postductal P_{aO_2} levels up.

Thompson: I'd like to echo what Jay (Roberts) just said about getting a call for a patient who's prone, on high frequency ventilation, and getting NO: please come and pick him up for ECMO. We, obviously, can't do that. We can't even do high frequency ventilation in transport. So, it is a real problem for us transporting patients. I'd like to ask Jay about getting a cardiac echo prior to the use of NO in neonates.

Roberts: I think that's critical to do, and that's part of the standard evaluation of cyanotic babies. This permits not only diagnosis of pulmonary hypertension but also of other structural cardiac lesions that might lead to extrapulmonary shunting and cyanosis. Getting an echo to diagnose pulmonary hypertension prior to the use of NO has been built into many of the experimental protocols that have evaluated INO in newborns. But I think that as time goes on, and NO becomes more available, they'll use NO as a trial to diagnose pulmonary hypertension. So, if NO is given to certain babies, and there is increase in systemic oxygen levels, they'll say, well, we can't rule out a cardiac lesion, but there is, to some degree, some extrapulmonary shunting and vasoconstriction that we're treating.

Thompson: Isn't there a fear that they have left ventricle dysfunction, and their systemic circulation is by their right ventricle, and that giving NO will devastate them?

Roberts: Well, I think that that can be a concern, but it is unlikely, and easily reversible with discontinuation of INO.

Pearl: Going back to the issue of dosing: I've always had trouble in individual cases knowing whether, when people tell me a patient required 80 ppm vs 20 ppm, they were seeing true effect or just variability. Do you believe that there are babies who do require the 80 ppm, and, if so, why do you think they require high doses?

Roberts: I think that most of the babies who have an increase in postductal P_{aO_2} with 80 ppm will also have some effect with 20 ppm, although it might be smaller, so I don't want to say that 80 is mandatory in those babies. One of the other problems I want to mention has to do with the onset time. In the lamb model we observed that the onset time could be very rapid, but Hallman[1] and his group looked at the onset time of INO in babies with PPHN and found that you might not get the maximum effect of NO until after 20–30 minutes.

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Rich: I'm not familiar with this patient population as much as with adults, but in adults there's quite often a positive response in the parts per billion range, and I was just wondering if there is some similar type of dose response in the patient population you're talking about. Also, getting back to what Dr Pearl was talking about with rebound, if you find it beneficial to decrease the NO level as low as possible, maybe below 1 ppm or even 100 ppb before you wean in order to help prevent rebound?

Roberts: I don't think that this has been fully evaluated in newborns. That is, the dose response to very low levels, say less than 5 ppm NO, or the efficacy of maintaining a baby in the ppb range. But, anecdotally, I can say that some babies are extremely sensitive to low levels of INO, less than 1 ppm. And I can say it anecdotally because the original systems that we used to deliver NO used a Bird Blender that permitted NO delivery at this range. In some babies we observed a small increase in P_{aO_2} with this low level of NO. Nevertheless, the response was much lower than we observed at INO levels above 20 ppm.

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Pediatric Applications of Inhaled Nitric Oxide

John Thompson RRT, Scot T Bateman MD, and Peter Betit RRT

Introduction
Use of INO in Asthma
Use of INO in Pediatric ARDS
Use of INO in Chronic Lung Disease
Summary

[Respir Care 1999;44(2):177–182] *Key words: nitric oxide, NO, vasodilation, pediatrics, neonatology, acute respiratory distress syndrome, ARDS, asthma, pulmonary.*

Introduction

Lung pathology remains the most significant factor in morbidity and mortality in the pediatric intensive care unit. Primary respiratory failure in children is the most common pathway leading to cardiopulmonary arrest, and research on childhood respiratory failure is an area of active clinical investigation. Inhaled nitric oxide (INO) has recently generated a lot of attention in the pediatric intensive care community. Recent studies have demonstrated that neonates with meconium aspiration syndrome and/or persistent pulmonary hypertension treated with INO had decreased extracorporeal membrane oxygenation (ECMO) utilization.[1] This use of INO in neonates has been viewed as a first step in the use of INO in other pediatric (non-neonatal) lung disease. Nitric oxide's ability to cause pulmonary vasodilation and improve ventilation/perfusion matching makes its use promising in pediatric diseases which involve hypoxia or pulmonary hypertension, such as asthma or acute respiratory distress syndrome (ARDS). The literature on the use of INO in pediatrics is limited by the low incidence of significant lung pathology in children. Therefore, a large proportion of the INO data must be extrapolated from adult literature. Most of the pediatric studies are small series examining the effects of INO on hemodynamics and oxygenation, and no large randomized controlled studies have been published.

Use of INO in Asthma

Airway hypersensitivity secondary to asthma and infection continues to rise in prevalence and is still the number one reason for admission to our institution. There has been a recent proliferation of new treatment modalities for asthma, including longer-acting β_2 agonists, leukotriene inhibitors, and improved inhaled steroids. Respiratory failure as a result of asthma is still uncommon, but there is a subset of patients who die from previously well controlled asthma. The role of NO in asthma is currently being evaluated, first by examining the levels of endogenous NO and its relationship to airway responsiveness, then by studying INO's ability to bronchodilate airway smooth muscle.

Several studies have examined the level of expired NO in patients with asthma. Massaro et al[2] compared expired NO levels in 43 adult mild asthmatics to 90 healthy subjects, and found significant NO elevation in the asthma group (13.9 ppb vs 6.2 ppb, $p < 0.001$). In 7 of the asthma patients they found a significant reduction in exhaled NO after glucocorticoid treatment. Massaro's follow-up paper on intubated patients found that the increased NO in asthmatics was due to increased lower airways production, not nasopharyngeal contamination.[3] These findings were corroborated by Kharitonov et al,[4] who measured exhaled NO from bronchoscopy samples at different levels of the lung airway. Similar differences in exhaled NO have been found in childhood asthma, and the levels also decrease with anti-inflammatory treatment.[5,6,7] It has been postulated that NO may be released in inducible NO synthase, which is a product of airway inflammation. Stimulated macrophages, fibroblasts, neutrophils, smooth muscle cells, airway epithelial cells, and type II alveolar epithelial cells all have inducible NO synthase. Measurement of expired NO might become a standard marker of severity and response to

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treatment in many cases. However, de Gouw et al,[8] found that the level of expired NO decreased (instead of increased) after direct bronchoconstriction challenge. Overall, the latter reports suggest the possibility that exhaled NO could act as a measurement of asthma treatment response if the asthma is mild and the patient has adequate air flow. The utility of exhaled NO measurement in more severe asthma cases remains unclear, especially if worsened airway constriction causes a lower exhaled NO level.

INO as a treatment for asthma has also been studied. Despite the fact that inflamed airways in asthmatics tend to have elevated NO levels, administering INO might provide some therapeutic benefit. The elevated NO in asthmatics is most likely the product of inducible NO synthase, and might actually inhibit the production of constitutive NO synthase. Constitutive NO synthase produces NO in areas where it might directly cause smooth muscle relaxation, and/or act as a neurotransmitter for nonadrenergic, noncholinergic (NANC) nerve mediated bronchodilation.[9] NO appears to be the main mediator of NANC relaxation.[10] By treating asthma with INO, the theory is that the NO will reach the areas where it is being suppressed.

Animal studies have shown that INO reverses methacholine-induced bronchoconstriction.[11] Kacmarek et al[12] studied 13 adults with mild asthma by administering methacholine challenges until their FEV_1 dropped $> 20\%$ and then treating them with 100 ppm INO for 10 minutes. Repeat pulmonary function tests (PFTs) done during and after INO treatment found a small but significant increase in FEV_1, but also found that 6 of the patients were responders and had a $> 15\%$ response. The increases were sustained even after discontinuing INO.

Pfeffer et al[13] studied 12 children with mild to moderate asthma using PFT measurements. All the children had baseline PFTs, followed by 15 minutes of 40 ppm NO via mouthpiece, then another PFT 10 minutes later, and finally a fourth PFT measurement after a treatment with aerosolized albuterol. There was no difference from baseline with the INO treatment, but the albuterol treatment caused marked improvement. No studies have been published on the use of INO in intubated or even hospitalized patients with asthma. The benefit of INO in the treatment of asthma remains unclear and needs further study.

Use of INO in Pediatric ARDS

Severe respiratory failure in children remains relatively infrequent, with an incidence reported to be 8.5–10.4/1000 admissions to pediatric intensive care units.[14] ARDS in children has been associated with a mortality rate as high as 50% to 70%.[15,16,17] Recent reports have indicated survival rates of up to 65%.[18] The pathophysiology of ARDS in children is essentially similar to that of adults, and is defined by the same hemodynamic and oxygenation indices.[16,17] Specifically, ARDS is characterized by impairment of the alveolar-capillary membrane which causes increased permeability and edema.[16,17] Varying degrees of pulmonary vasoconstriction occur and lead to elevated pulmonary artery pressure and right-sided heart failure.[16,17] The increased alveolar-capillary permeability, coupled with pulmonary vasoreactivity, causes an abnormal ventilation-perfusion relationship, resulting in hypoxemia.[16,17] Clinical diagnosis of ARDS typically includes positive end-expiratory pressure (PEEP) requirements of > 6 cm H_2O and fraction of inspired oxygen (F_{IO_2}) > 0.5 for 12 or more hours, diffuse bilateral infiltrates on chest radiograph, and the ratio of arterial oxygen tension (P_{aO_2}) to F_{IO_2} is < 200 mm Hg.[16,17] Children usually have less ischemic cardiac involvement, but isolated lung pathology is common. Similar to the adult experience, INO can be an important adjunct in the clinical management of pediatric ARDS. It has been demonstrated that INO reduces pulmonary vascular resistance and associated pulmonary edema, enhances the ventilation/perfusion relationship, and therefore aids in minimizing oxygen and ventilation requirements.[19–24]. The use of INO in the management of ARDS in children has been evaluated in several reports (see Table 1).

Abman et al[19] looked at the effect of INO in 10 pediatric patients with ARDS (mean age 7 years) and 7 patients with viral pneumonitis (mean age 4 months). The patients were mostly treated pre-therapy with very high ventilator settings, with mean levels of PEEP 12 cm H_2O, airway pressure 25 cm H_2O, and F_{IO_2} 0.93. Within 30 minutes of initiation of INO, P_{aO_2} levels increased by 50% in each group ($p < 0.01$), with 15 out of the 17 responding to the therapy. The effect was improved by increasing the INO concentration from 10 ppm to 20 ppm, but increasing it from 20 ppm up to 40 ppm did not further improve the oxygenation effect. In 10 patients who had pulmonary artery (PA) catheters in place, mean PAP was lowered from 72 to 31 mm Hg ($p < 0.01$), and intrapulmonary shunt fraction decreased ($p < 0.01$). There was no change in arterial carbon dioxide tension (P_{aCO_2}) or pH, and mortality was 50%. This report concluded that there is an acute improvement in gas exchange and hemodynamics with the addition of INO, and it suggested that INO enhances ventilator management strategies by allowing the reduction of ventilator volumes and oxygen concentration. No significant adverse effects were observed.

Nakagawa et al[25] studied 14 children (mean age 63 months) with ARDS, all with an oxygenation index (OI) of over 10 (mean OI of 34), and mechanical ventilation for a mean of 48.5 hours. PA catheters were used in children over 10 kg (10 patients). INO was titrated in 10-minute intervals, from 10 ppm up to 20 ppm, from 20 ppm up to 40 ppm, from 40 ppm up to 60 ppm, and from 60 ppm up to 80 ppm, recording data at each time point. The patients

Table 1. Summary Clinical Data for the Use of Inhaled Nitric Oxide in Pediatric Acute Respiratory Distress Syndrome

Author	Population	Initial INO Dose	Overall Mortality	Findings
Abman et al[19]	10 ARDS 7 viral pneumonitis	10 ppm	50%	Acute improvement in gas exchange. INO permits the lowering of ventilator settings. Non-ARDS patients had better response.
Nakagawa et al[25]	14 ARDS	10–80 ppm	38%	Significant decrease in OI. Maximum beneficial dose = 20 ppm. Decreased PVRI.
Demirakca et al[22]	8 ARDS	20 ppm	0%	Significant decrease in OI. Overall improvement in gas exchange. Discontinuing INO best tolerated when OI < 5.
Day et al[20]	19 ARDS	11 or 60 ppm	45%	Improved P_{aO_2}/F_{IO_2}. Decreased PVRI. Chest radiograph identifies responders.
Goldman et al[24]	30 ARDS	20 ppm	60%	Significant decrease in OI. All patients with < 15% response died. Mortality least with > 30% response.
Day et al[21]	24 ARDS	10 ppm	46%	Acute improvement in OI. Sustained treatment has limited role. Lowest effective dose 10–20 ppm.

ARDS = acute respiratory distress syndrome; OI = oxygenation index; PVRI = pulmonary vascular resistance index; ppm = parts per million.

continued to receive the lowest dose of INO that gave a positive response, and then the INO was tapered at the discretion of the intensive care unit staff. Seven out of 10 children with PA catheters had a positive response, with a decrease in pulmonary vascular resistance index (PVRI) of 30% or greater, but did not reach statistical significance. There was a significant decrease in OI and increase in P_{aO_2}, with the maximal benefit found at 20 ppm INO. Five children were non-responders. It was suggested that the lack of response might be associated with poorly recruited lung volume. It was also suggested that concentrations greater than 40 ppm might result in worsening ventilation/perfusion matching due to the presence of irreversible pulmonary vasoconstriction. No additional benefit beyond the initial treatment was found, and the mortality was 38%.

Another dose-response study was conducted by Demirakca et al.[22] Eight pediatric patients (mean 1.75 years) with ARDS were evaluated after treatment with INO in concentrations ranging from 1 to 80 ppm. All 8 patients had OIs greater than 25 and a mean duration of mechanical ventilation of 3.5 days. All 8 patients were started at 20 ppm for one hour and then had dosing alterations. They demonstrated a significant improvement in OI and P_{aO_2}, as well as P_{aCO_2} and pH. There was only 1 nonresponder. Among these 8 patients, 10 ppm INO was the lowest effective dose. All of their patients survived to discharge. These investigators noted a continuous improvement in oxygenation with prolonged inhalation (4–21 days) and identified an OI of under 5 as a predictor of successful weaning from INO (sensitivity 75%, specificity 89%).

Day et al[20] studied 19 pediatric patients (ages ranging from 7 months to 16 years) using an initial randomized INO dose of 11 ppm and 60 ppm, followed by continuous therapy with either 10 ppm or 40 ppm INO. The therapeutic doses of 10 or 40 ppm were selected based on previously-observed high methemoglobin levels when 60 ppm was used for prolonged periods. This study demonstrated an improvement in P_{aO_2}/F_{IO_2} and PVRI/systemic vascular resistance index (SVRI) with serial exposure to INO. It was suggested that the greatest response was associated with radiographic evidence of residual aerated lung regions. A sustained improvement in P_{aO_2}/F_{IO_2} was observed with prolonged therapy, and INO was discontinued with PEEP levels decreased to 6 cm H_2O and F_{IO_2} requirements to 0.50. Methemoglobin levels were elevated in patients who received 40 ppm INO (3.0 ± 0.3%) compared to those who received 10 ppm INO (1.6 ± 0.01%). The duration of ventilation in this group was 16 ± 3 days, and mortality was 45%. This study demonstrated a moderate improvement in oxygenation with the initial randomized doses and a sustained effect with prolonged therapy. It was suggested that the chest radiograph might help determine which patients will have a better response. Patients with more diffuse or complete infiltrates might respond less than those with residually aerated lung regions.

Goldman et al[24] conducted a study to determine the effect of INO on pediatric ARDS outcome. They examined the hypothesis that the magnitude of the acute response to INO might suggest reversible lung disease. Thirty patients with ARDS received a trial of 20 ppm INO for 1 hour, and the patients were then considered as 3 groups: < 15% change in OI, 15–30% change in OI, and > 30% change in OI. The INO was then continued at the discretion of the attending physician. The mean OI prior to the therapy was 41, and mean duration of mechanical ventilation was 8.4 days. Ten patients were on high-frequency oscillatory ventilation, and 5 received surfactant therapy. Overall, there was statistically significant improvement in oxygenation data after beginning INO. All 6 patients with < 15% response died, 7 of the 11 patients with 15–30% response died, and 5 of the 13 patients with > 30% response to INO died ($p < 0.02$). Overall mortality in this entire patient population was high, at 60%.

The only randomized controlled study published to date on INO in pediatric ARDS was by Day et al.[21] Twenty-four pediatric patients (mean age 7 years) with ARDS (bilateral infiltrates, $F_{IO_2} > 50\%$, and PEEP > 6 for over 12 h) were enrolled within 48 hours of meeting criteria. In the first 24 hours of the study, patients received 10 ppm INO or conventional treatment, and after the initial 24 hours all patients received 10 ppm INO. They found a significant improvement in OI, by 17 ± 4%, after the first hour, comparing INO to nitrogen gas placebo. The effect, however, was not sustained after 24 hours of treatment. The INO group also had 9 out of 12 patients convert to high frequency oscillatory ventilation after randomization, compared to none in the control group. Only 7 of 12 randomized to INO were responders demonstrating a > 20% response to treatment. Five of these patients sustained the improvement at 24 hours, but this was compared to 4 of 12 patients in the control group who had a > 20% improvement. After the initial 24 hours, the control group received INO, and had a sustained significant improvement in OI at 1 hour, which was sustained 24 hours later. The overall mortality in the study population was 46%. Interestingly, 7 deaths occurred while receiving INO, and 6 of them were responders during the initial hour of treatment. This study suggests that INO might have a limited therapeutic role in children with acute hypoxemic respiratory failure. No therapeutic controlled study beyond 24 hours has been done on this subject.

It is clear from the data presented that INO has significant acute effects on oxygenation and pulmonary hypertension for the majority of pediatric patients with ARDS. The lowest effective dose appears to be between 10 and 20 ppm INO. The improved oxygenation effects are almost instantaneous clinically (within 10 minutes of initiation of INO). The only placebo-controlled study, however, suggests that the effect might not last beyond the first hour. The effect on outcome remains to be established. In fact, a responder to INO treatment might eventually be used for prognostic purposes, or might help stratify patients into different treatment strategies. Short-term risks appear to be low. No significant methemoglobinemia or nitrogen dioxide levels were noted in any of the treatment groups who used 20 ppm INO or less.

Use of INO in Chronic Lung Disease

Chronic Lung Disease (CLD) continues to be a common sequela in the management of extremely premature infants.[26,27] The incidence of CLD varies widely and is associated with prolonged ventilator duration and supplemental oxygen.[26,27] One complication of CLD is the development of increased pulmonary vascular resistance leading to right-heart strain and eventual failure.[26,27] Since INO has pulmonary vasodilator qualities, it has been suggested that it might be beneficial in the management of CLD. A few case series have been reported.

Lonnqvist et al[28] administered INO to 9 infants with CLD. Concentrations of 6, 10, 30, and 60 ppm INO were delivered for 10-minute intervals. A significant improvement in oxygenation was observed, as evidenced by a reduced OI. The optimal dose response varied among patients, and was attributed to the varying degrees of CLD, with some patients possibly having more vascular abnormalities. No change in P_{aCO_2} was observed in this study, which might be due to the presence of dead space in overexpanded lung regions. The effect of INO on cardiac function was unattainable, and there were no significant adverse effects, including methemoglobinemia and prolonged bleeding times. The investigators suggested that randomized studies of prolonged therapy and outcome were warranted.

In Abman's series,[19] described above, 6 CLD infants with viral pneumonitis were included. Their ventilator requirements were significant for mean airway pressures of 20 cm H_2O, and baseline P_{aO_2} was 49 ± 11 mm Hg. The administration of 20 ppm INO resulted in an increase of P_{aO_2} to 76 ± 13 mm Hg (50% improvement), and subsequent reductions in F_{IO_2}, by 0.17 ± 0.11. The survival rate for these patients was 100%. It was suggested that INO might be beneficial in non-ARDS respiratory failure such as infants with CLD who acquire viral pneumonitis.

Similarly, Thompson et al[29] treated a 2-month-old infant with bronchopulmonary dysplasia infected with respiratory syncytial virus. On admission this patient required inflation pressures of 37 cm H_2O and the OI was 53. A trial of high frequency oscillatory ventilation was attempted, but F_{IO_2} requirements were still 0.80. INO at 40 ppm was delivered and oxygenation immediately improved with F_{IO_2} requirements reduced to 0.50, and OI decreasing to 21. The duration of INO therapy was 6 days, and the patient was successfully weaned from ventilatory support, and was extubated on day 9. The use of INO in this patient improved oxygenation, allowed the reduction of ventilator settings, and prevented the need for extracorporeal life support.

The use of INO in patients with CLD may be beneficial in improving gas exchange when additional pulmonary insults from infection occur. This might allow the use of less harmful ventilator settings and oxygen concentrations that could otherwise further worsen the patient's underlying chronic condition. It is not clear if INO will lower pulmonary vascular resistance enough to improve right-heart function, or if INO will help remodel pulmonary vasculature.

Summary

The use of INO therapy in pediatrics remains in its infancy. As with many other interventions in the pediatric intensive care unit, it will be extremely difficult to gather the numbers needed to get well-controlled and randomized data in the pediatric population. However, the data presented thus far are promising and merit further study. Exhaled NO appears to be a marker of airway inflammation in many cases. INO does not appear to be effective in milder asthma, but needs to be studied in severe asthma to better assess its efficacy when more severe airway disease is present. In pediatric ARDS, INO improves oxygenation and should allow lower mechanical ventilation support and lessen complications. No clear outcome benefit has been demonstrated yet, but further well-controlled study is needed. The data suggest that a subset of patients are nonresponders to INO. This subpopulation could eventually be significant because it might represent a subset who need better lung recruitment strategies. Similarly, in children with CLD, INO appears to a promising treatment option, but needs more study. Patients with pre-existing right ventricular work overload and pulmonary hypertension seem particularly needy of the benefits of INO when confronted with a new pulmonary crisis. In addition to the 3 areas discussed in this review, the use of INO in the pediatric ICU continues to be expanded. Areas of active INO research include treatment of sickle cell disease, especially the acute chest syndrome,[30] the management of postoperative congenital heart disease,[31,32] and lung transplantation.[33,34,35] The data presented in this review show that using INO in pediatric patients appears to be safe. No significant adverse effects were reported, although the numbers were small in each paper. INO should continue to be studied in the pediatric population.

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Discussion

Hurford: At Children's Hospital (Boston) when a child comes in with respiratory syncytial virus pneumonia, or something like that, do they get INO as part of their therapy?

Thompson: Probably not. It's not part of our protocol to use NO with RSV pneumonia. Is it your protocol to use it?

Hurford: No. What about in other forms of acute lung disease in children? Do you think you'll use it just in newborns and then have a cutoff on a particular age, or should you have a cutoff for a particular type of disease? What are you using to differentiate this intermediate population from a newborn population?

Thompson: I don't think we sit down and do that. Let me give you my biased thoughts. I think that the increased muscularization of the pulmonary vasculature that Jay (Roberts) spoke of that may be obstructive in newborns, may be very helpful in the pediatric patient; not necessarily the 300-pound, 16-year-old boy, but more toward the 6-month and the one-year old. I believe we're probably going to see a better response to NO than in the adult population because of this increased muscularization of the pulmonary vasculature. So, we don't stratify them in any way right now, but I think we will.

Hess: Another way of looking at this is extrapolating from the adult experience to the pediatric experience. I don't think there have been any controlled trials on NO and pediatric ARDS, and I suspect maybe there won't be any. What are the dangers, or is it appropriate to extrapolate the results of the adult trials of ARDS to children with ARDS?

Thompson: Yes, I think the ARDS basket of diagnoses is the same in pediatric patients as in adults. I don't think you would look at our criteria for ARDS (PEEP of 6 in 50% F_{IO2}) as your criteria. I don't know of the dangers of extrapolating the adult experience. For us to get any significance, it's going to have to be multi-center, randomized trials. But I don't think we're going to do that.

Channick: Just a follow-up. I guess when you determine that it's extrapolating, it's really going to come down to etiologies of ARDS. I'm sure we'll get into this a lot more in the next talk, but, theoretically, in diseases where primary lung injury is the predominant pathophysiology, NO is more likely to beneficially alter outcome, and so I guess we would ask what would be the typical etiologies of pediatric ARDS? Is it sepsis and trauma, like we see in adults?

Thompson: I'd have to say all those are pretty much the same. I think the one difference that we see that you don't see is primary pulmonary diseases. We don't see as much of the multisystems failure that you probably see. We don't have patients coming in after 20 years worth of hamburgers and french fries and heart conditions like that. We treat patients with strong hearts and diseased lungs.

Head: Most of your NO work is with congenital heart disease. Is that correct?

Thompson: Correct.

Head: I am curious regarding your protocol. At what point in time did you initiate NO in these patients? Before surgery, during surgery, or after surgery? And at what dose do you start it?

Thompson: We are still at the 80 ppm testing. So all of our patients have an initial trial of 80 ppm. It depends on the patient population. We have about 30% of our patients in the cath lab. Most of the other patients are preoperative or postoperative.

Head: So you're not using it intraoperatively?

Thompson: Very seldom. The only time that we really get called down to the operating room is when they can't get off the pump.

Bigatello: I have a question on one of the 3 categories that you discussed: the chronic lung disease. You showed some very nice results with NO decreasing the F_{IO_2} and the oxygenation index, which is probably actually a little better than in the adult experience. But I think we've seen a nice response in many applications of NO. What I am getting increasingly concerned about clinically is how long the response lasts. Are any of your studies long-term? Did these patients actually get off the ventilator and continue to get better on NO, or was this a spot-check result?

Thompson: Most of them were spot checks and not long-term. Our mortality rate has not changed. I don't think we're getting patients off much better with NO. Our mortality rate is still as high.

Pearl: The last line of your text had an intriguing statement, "help remodel pulmonary vasculature." That's clearly of interest for adult pulmonary hypertension patients, and I suspect Dr Channick will discuss some of that, but could you expand on it? Was that just a conceptual possibility, or are there some data in the pediatric population?

Thompson: We have some data: a total of 4 patients with infantile primary pulmonary hypertension. Three of them have been published.[1] Those patients were put on long-term 25-day NO. And with what would be a lethal disease, we had 3 of the 4 survive. In fact, at day 25, the pulmonary vascular resistance had dropped dramatically, and as far as a year out continued to stay low.

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Hess: I'd like to get back again to INO in bronchopulmonary dysplasia. I don't take care of kids much, but I think of bronchopulmonary dysplasia as being like chronic obstructive pulmonary disease in adults, and the literature, as I understand it, as far as INO in chronic obstructive pulmonary disease, is that it many times does not improve oxygenation. I guess that's been attributed to getting the NO into areas of low ventilation-perfusion and increasing blood flow to those areas, and thus making the ventilation-perfusion worse. Any comment on that?

Thompson: Again, no data, but I certainly have comments, and that is that the alveolar wall destruction that you see in chronic obstructive pulmonary disease we certainly have in bronchopulmonary dysplasia also, and those areas that have a very high dead space, I don't think those patients with severe bronchopulmonary dysplasia are going to respond to NO. I think the Lönnqvist paper,[1] indicated that the more chronic lung disease they had, the less they responded.

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Hurford: We have a series[1] of about 7 or 8 children with bronchopulmonary dysplasia that we've looked at short-term, presented as an abstract, that had an absolutely unappealing response to INO: basically no effect at all in any of the children as far as acute oxygenation, hemodynamics, or anything else. Echoing that these children probably have fixed disease, high dead space, and it's probably an inappropriate treatment for this type of disease.

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Thompson: Did any of them have a negative effect?

Hurford: No.

Inhaled Nitric Oxide for Acute Respiratory Distress Syndrome

Marlene Gerlach MD, Didier Keh MD, and Herwig Gerlach MD

Introduction
Nitric Oxide Inhalation in ARDS: First Trials
Adverse Effects
Review of Controlled Studies
INO Dose Levels in ARDS
Theories of NO Transport
Summary

[Respir Care 1999;44(2):184–192] *Key words: nitric oxide, NO, acute respiratory distress syndrome, ARDS, inhaled nitric oxide.*

Introduction

Acute lung injury and its aggravated form, acute respiratory distress syndrome (ARDS), is characterized by a sudden, mostly generalized inflammation of the lung, which, in the further course, induces (1) non-cardiogenic pulmonary edema, (2) pulmonary arterial hypertension, (3) reduction of total compliance of the lung, and 4) progressive systemic hypoxemia due to a pulmonary ventilation/perfusion-mismatching, leading to an increased intrapulmonary right-to-left shunt area. Pulmonary hypertension causes a rise of the microvascular filtration pressure in the lung and, therefore, development of an interstitial pulmonary edema, as well as overstress and dysfunction of the right ventricle. Until recently, the only therapeutic means of re-establishing a safe level of oxygenation in patients with ARDS was mechanical ventilation with high inspiratory oxygen concentrations (fraction of inspired oxygen [F_{IO_2}]) and positive end-expiratory pressure (PEEP). Such an approach could be counter-productive in some patients because high O_2 concentration and high airway pressure can cause further lung damage due to O_2 toxicity and pulmonary barotrauma. A pharmacologic approach is emerging as an adjunct to conventional management, and aims to decrease the need for high O_2 concentrations and high airway pressures. The objective of most of these newer modalities is to redistribute the pulmonary blood flow preferentially toward well-ventilated alveoli.

Ventilation-perfusion mismatch is one of the hallmarks of ARDS. In the lung, regions of normal ventilation/perfusion ratio (V/Q) coexist with regions of low V/Q. A large proportion of the lung, which appears ventilated on chest radiograph and computerized thoracic scan, is poorly perfused or not perfused at all (alveolar dead space). At the same time, part of the nonventilated zones continue to be perfused due to the failure of hypoxic pulmonary vasoconstriction (HPV), a reflex which tends to limit the pulmonary blood flow perfusing poorly oxygenated alveolar spaces. High tidal volumes (V_T) and, consequently, high airway pressures are needed to maintain normal arterial carbon dioxide tension (P_{aCO_2}) in the face of increased alveolar dead space.

Acute pulmonary hypertension, which is frequently observed in patients with ARDS, is a result of pulmonary vasoconstriction characterizing the early stages of ARDS, and of the remodeling of pulmonary vasculature that is observed in the late stages of ARDS. This pulmonary vasoconstriction can, in turn, be due to the HPV reflex or chemical mediators such as thromboxane A_2 and platelet activating factor. Anatomical remodeling consists of muscular hypertrophy, microthrombosis, fibrosis, and destruction of pulmonary vessels. Theoretically, selective constriction of the pulmonary vessels in the nonventilated zones or selective vasodilation in the ventilated zones should decrease the V/Q mismatch. Administration of selective pulmonary vasoconstrictors and vasodilators is the basis of the pharmacologic approach to hypoxemia during ARDS. Ideally, these vasoactive drugs act on the pulmo-

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nary circulation while having little or no effect on systemic circulation.

Nitric oxide (NO) is a multipotent endogenous messenger molecule that is extensively involved in the regulation of vascular tone. NO is also a well known environmental pollutant, emanating from internal combustion engines and factories. NO is toxic in higher concentrations, and the legal limit for NO occupational exposure is 25 parts per million (ppm). However, NO gas mixed in nitrogen can be used for medical purposes as an inhalable drug, administered together with the inspiratory gas. NO passes through the alveolar membrane and reaches the blood in the pulmonary vasculature, where it is taken up and possibly absorbed by hemoglobin before it reaches the systemic circulation. Inhaled NO (INO) is considered a selective pulmonary vasodilator because it dilates the pulmonary vasculature that is in contact with ventilated alveoli, while having no effect on the resistance of the systemic vasculature.

Nitric Oxide Inhalation in ARDS: First Trials

Furchgott and Zawadzki were the first to describe the in vitro phenomenon that vascular relaxation requires the presence of an intact vascular endothelium.[1] Later, NO was identified as the active agent of endothelium derived relaxing factor.[2,3] Characterization of NO synthesis and the pathophysiologic pathways of NO vasodilation quickly followed.[4,5] Meanwhile, NO was also found to be synthesized by brain cells, macrophages, epithelial cells, and platelets, acting as a neurotransmitter, mediator of cellular immunological processes, and modulator of platelet aggregation and adhesion, for example, during inflammation.[6] However, NO is not only a physiologic mediator, but also an environmental gas that results from combustion, and quickly oxidizes into NO_2. NO is extremely lipophilic and tends to bind to the ferruginous heme group. After inhalation, exogenous NO freely diffuses into the alveolar capillaries and within seconds binds to the heme group of hemoglobin with a 1,500-fold higher affinity than carbon monoxide.[7] The resulting nitrosyl-hemoglobin is unstable, oxidizes to methemoglobin, and transforms to nitrates. The nitrates are metabolized unspecifically and excreted through the kidneys.

When the biological relevance and the physiologic pathways of NO became clear, the question arose as to whether gas-phase NO might have a therapeutic use. It was theorized that INO, similar to endogenous, endothelium-derived NO, should be able to induce vasodilation. And because NO binds rapidly to hemoglobin, within seconds of diffusing into the intravascular space, INO might be inactivated immediately without influencing the systemic circulation, thus acting as a selective pulmonary vasodilator. Animal studies (lasting as long as 6 months) on the toxicity of INO found no evidence of adverse effects using NO doses of less than 40 ppm.[8,9] The first pilot studies in humans, conducted by Higenbottam et al in 1988, demonstrated that the inhalation of NO was, indeed, able to reduce pulmonary hypertension in adult patients without major effects on the systemic circulation.[10,11] Animal experiments by Frostell and Pison revealed that INO was also able to reverse hypoxic pulmonary vasoconstriction without impairing pulmonary gas exchange.[12,13] Two other research groups found that INO can be useful in treatment of persistent pulmonary hypertension of the newborn.[14,15] In all these studies, INO was administered at doses ranging between 5 ppm and 80 ppm, and no critical adverse effects such as systemic hypotension or methemoglobinemia were observed.

Falke et al conducted the first INO treatment of ARDS patients, using doses of 18 ppm and 36 ppm. The observed effects on hemodynamics and pulmonary gas exchange were compared with the effects after treatment of the same patients by intravenous infusion of prostacyclin (PGI_2), using a dose of 4 ng/kg/min.[16] Later research by Rossaint et al revealed that both INO and infused prostacyclin can reduce pulmonary vascular resistance by about 20%.[17] While INO did increase arterial oxygenation significantly, it did not induce any significant change in systemic hemodynamics, in contrast to prostacyclin, which caused systemic hypotension and a decrease of arterial oxygen saturation (Fig. 1). Measuring the ventilation/perfusion ratio by multiple inert gas elimination technique, it was found that intrapulmonary shunt area was increased by infusion of prostacyclin. By contrast, inhalation of 18 and/or 36 ppm NO decreased the area of intrapulmonary shunt, because of redistribution of pulmonary blood flow toward areas with nearly normal ventilation/perfusion ratios. Daily tests of INO efficacy using a 20-minute shut-off followed by re-administration of NO inhalation (so-called "on-off-on measurements") found that this beneficial effect of INO was also observed in long-term studies with doses of less than 20 ppm INO.[17] Severe adverse effects, especially the formation of toxic metabolites of NO such as methemoglobin or nitrogen dioxide (NO_2) were not observed, even during long-term INO treatment.

Adverse Effects

During several clinical trials it was reported that, especially after long-term INO treatment, patients need a special weaning procedure to terminate NO inhalation. Rebound phenomena regarding both systemic oxygenation and pulmonary hypertension indicate that patients can develop INO dependence.[18] These effects are probably due to inhibition of the endothelial nitric oxide synthase (NOS) by the exogenously supplied NO, which was demonstrated in vitro using NO donors,[19] as well as gas-phase NO.[20]

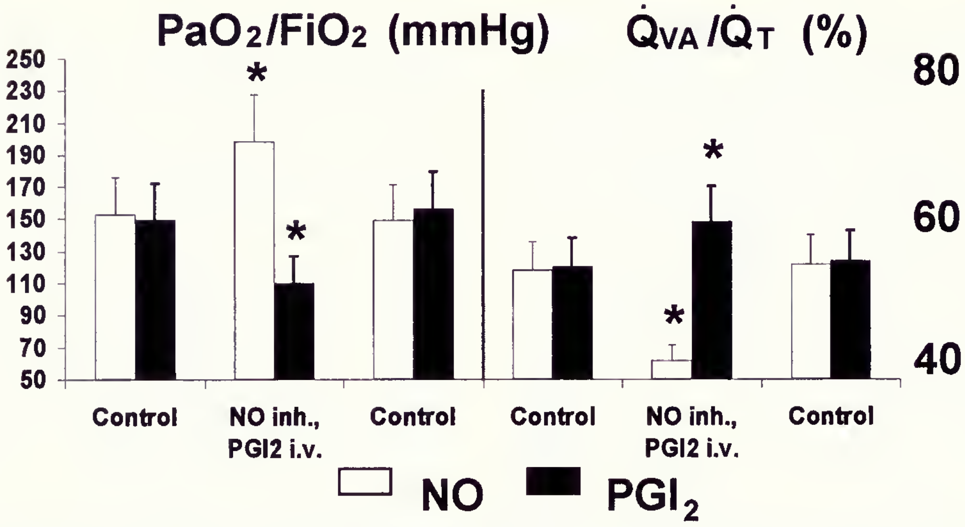

Fig. 1. Effect of inhaled nitric oxide (NO inh.) (18 parts per million) versus intravenous prostacyclin (PGI$_2$ i.v.) on systemic oxygenation (P_{aO_2}/F_{IO_2}) (left side of figure) and venous admixture (Q_{VA}/Q_T) (right side of figure). Compared to controls before and after measuring the effect, PGI$_2$ i.v. (black bars) decreased P_{aO_2}/F_{IO_2} by enhancing venous admixture. In contrast, inhaled NO (open bars) resulted in a significant improvement of systemic oxygenation by decreasing the intrapulmonary right-to-left shunt. (Modified from Reference 17, with permission.)

Thus, vasoconstriction in the ventilated areas may recur if NO is withdrawn suddenly.[20] These findings, combined with other studies showing that the absolute level of the pulmonary arterial pressure (PAP) is a marker for the severity of pulmonary microvascular injury in ARDS,[21] and that pulmonary hypertension is associated with impaired NO production,[22] support the hypothesis that even low doses of NO might reduce PAP in severe cases of acute lung injury because endogenous NO production by the pulmonary vascular endothelium is considerably impaired under these circumstances.[17,18] This was underlined by the observation that intravenous administration of inhibitors of endogenous NOS increases systemic and pulmonary vascular resistance in septic patients with vasoplegia, but has little or no effect in ARDS patients who had received INO for a longer period.

Other studies have found that administering INO prolongs bleeding time in animals and healthy humans[23,24] and inhibits platelet aggregation in patients with ARDS.[25] Case reports point to the danger of serious bleeding disorders arising from NO inhalation, which can lead to intracerebral hemorrhage and death.[26] In vitro, NO released from endothelial cells inhibits platelet-adhesion to endothelium,[27] inhibits platelet-aggregation,[28] and has disaggregating properties.[29] Endogenous NO, produced by a Ca^{2+} and NADPH-dependent cytosolic NO synthase (NOS) via the L-arginine/NO pathway, downregulates platelet aggregability. This was found to be an intra-platelet negative feedback mechanism that modulates platelet response after stimulation.[30,31] Similar to smooth muscle cells, the inhibitory effect of NO on platelets is mediated through cyclic guanidine monophosphate, which inhibits the phospho-inositide pathway regulating phospholipase C and indirectly increases cyclic adenosine monophosphate by inhibiting cyclic adenosine monophosphate-specific phosphodiesterase.[32] As a result of the interaction of NO with intracellular signal transduction, platelet aggregation decreases by inhibition of Ca^{2+}, release of granule contents, and phosphorylation of proteins.[33] Thus, NO plays an important role in regulation of vascular homeostasis by controlling vascular tone and platelet function.

Whereas NO-platelet interactions were intensively studied by numerous investigators using functional assays, measurement of secreted granule contents, ligand binding to receptors, and analysis of intra-platelet activation dependent metabolic pathways, little data exist about the effects of NO on platelet cell-surface adhesion receptor expression during activation with α-thrombin, as measured by flow cytometry.[34] Keh et al investigated the modulating effects of the NO releasing compound SIN-1[35] on the availability of different functional platelet adhesion receptors by flow cytometry.[36] Using a specific antibody (PAC) against the activated form of the fibrinogen receptor glycoprotein GP IIb-IIIa, it was found that SIN-1 has a dose-dependent inhibitory effect on GP IIb-IIIa activation. As well, the inhibition of α-thombin-induced platelet activation by SIN-1 was found to be possible up to 60 min after activation.[36] That is, in vivo, INO can induce bleeding disorders by disaggregating platelets, even when bleeding does not occur initially after surgical interventions. This is important in terms of defining inclusion and exclusion criteria for future clinical studies of INO in acute lung injury, although none of the controlled clinical studies

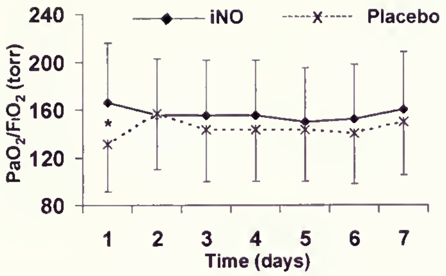

Fig. 2. Systemic oxygenation (P_{aO_2}/F_{IO_2}) values for the pooled inhaled nitric oxide (INO) treatment group (solid line) and placebo group (dashed line) over the first 7 days. Note that the beneficial effect of INO on arterial oxygenation is only significant (*) during the first 24 hours. (Modified from Reference 38, with permission.)

performed so far on INO treatment of ARDS patients has shown any increase in bleeding disorders (see below).

Review of Controlled Studies

The determination that INO reduces pulmonary hypertension and increases systemic oxygenation in ARDS patients led to the question of whether INO might be able to improve outcomes in terms of reducing mortality or intensive care unit ventilation time. Retrospective matched-paired analysis revealed that there was no difference in survival rate between ARDS patients who had received INO therapy and those who had not (survival rate in both groups was 69%). Further, no differences were found in the duration of ventilation or intensive care unit stay.[37] Recently, the first prospective randomized, double-blind, placebo-controlled, phase II, multi-center trial, involving 177 ARDS patients, was published by Dellinger et al to evaluate safety, physiologic response, and outcome parameters of different doses of INO (1.25–80 ppm).[38] The same type of ventilator and NO delivery system was used for each patient, and NO treatment was performed according to a strict protocol. During the first 4 hours after initiation of treatment, ventilator settings were not changed, and improvement of oxygenation reflected the acute effects of NO inhalation. In the time period after the first 4 hours, ventilator settings were adjusted to achieve the target oxygenation index. Sixty percent of patients responded to INO with ≥ 20% increase in arterial oxygen tension (P_{aO_2}) which allowed a reduction of F_{IO_2}. However, this change was significant only on the first day of treatment (Fig. 2), and the reduction of F_{IO_2} was modest (0.71 ± 0.14 vs 0.69 ± 0.13). In the NO group, the oxygenation index remained lower during the first 4 days, and mean PAP remained lower (~2 mm Hg) for 2 days. During the initial 4-hour observation period, however, 24% of the placebo group also had a ≥ 20% increase in P_{aO_2}. There were no differences between the NO and placebo group with respect to mortality or the number of days the patients survived after meeting oxygenation criteria for extubation. A post hoc analysis revealed that in the group receiving 5 ppm NO, the percentage of patients alive, as well as of patients weaned from mechanical ventilation at day 28 after study inclusion, was higher than in the placebo group. However, when 56 additional patients who were discontinued from NO treatment before meeting oxygenation threshold criteria (mainly due to death) were included in the analysis, mortality of the NO group was even higher (38% vs 30%).

A randomized trial by Micheal et al investigated acute effects of INO on oxygenation parameters in 40 patients with ARDS during the first 3 days of treatment.[39] Similar to the results from Dellinger et al,[38] INO therapy, compared to conventional therapy, increased P_{aO_2}/F_{IO_2} only during the first day. After 24 hours the two groups had an equivalent improvement in P_{aO_2}/F_{IO_2}, and during the 72 hours following inclusion, reduction of F_{IO_2} (≥ 0.15) was not significantly different with or without INO. Another 30 ARDS patients were enrolled in a randomized, controlled pilot study by Troncy et al.[40] Again, improvement of oxygenation and reduction of venous admixture was significant only during the first 24 hours of NO inhalation, and there was no significant difference between the NO group and controls with regard to the 30 day mortality or days of mechanical ventilation. Preliminary results from a European multi-center study of more than 200 patients with acute lung injury showed no improvement in survival or duration of ventilation with INO.[41] Furthermore, there was a more frequent incidence of renal failure in the NO group (35% vs 16%), which was one major reason to discontinue the study before the initial protocol was finished. The latter finding, however, is in contrast to the previously-mentioned studies,[37–40] none of which found adverse effects from INO on renal function or bleeding disorders.

In conclusion, when focusing on outcome, INO treatment seems to have no advantage for ARDS patients. However, aiming for the primary target of NO therapy (selective pulmonary vasodilation with subsequent improvement of systemic oxygenation and pulmonary hypertension), there was a sustained effect (probably more pronounced with low doses of INO) in the majority of patients within the first 24 hours of treatment, which allowed reduction of the ventilator settings for F_{IO_2} and airway pressure.

INO Dose Levels in ARDS

The first studies of INO for treatment of ARDS[17] found no significant difference between INO concentrations of 18 ppm and 36 ppm with regard to INO's effect on pulmonary resistance and systemic oxygenation. Patients developed no tachyphylaxis, but, rather, seemed to become dependent on INO, even when the course of the disease

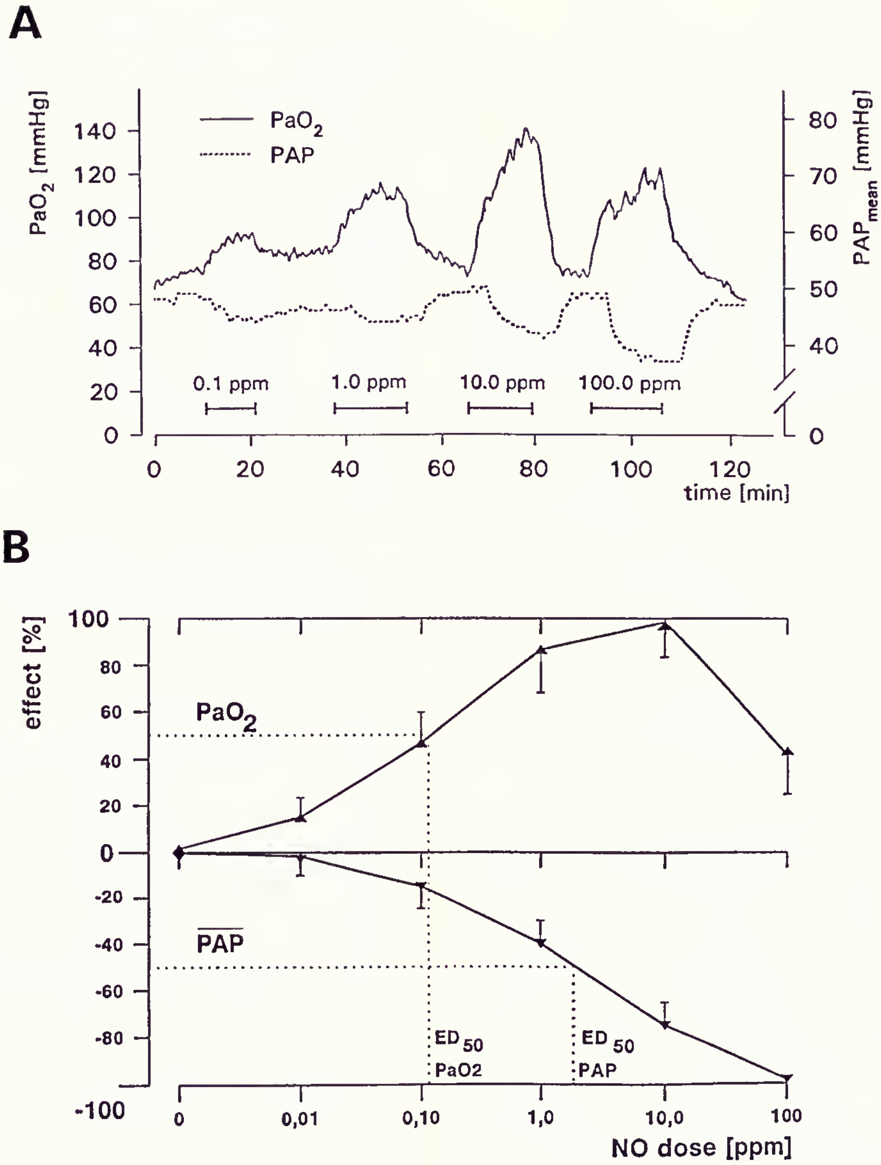

Fig. 3. Time course and dose response of inhaled nitric oxide (INO) for oxygenation and pulmonary artery pressure. A: Representative example for a continuous registration of arterial oxygen tension (P_{aO_2}) (solid line, left y-axis) and mean pulmonary artery pressure (PAP_{mean}) (dotted line, right y-axis) during inhalation of NO. Inhalation periods with the inspiratory doses of NO are indicated above the x-axis, which represents the time of measurement. B: Dose response for P_{aO_2} (upper part) and PAP (lower part) to inspiratory NO doses (x-axis). Values are means ± SD (n = 12), expressed as percentage (y-axis) of effect compared to the initial value (= 0% effect) and the highest registered alteration (= 100% effect). The estimated median effective dose (ED_{50}) of NO for improvement of arterial oxygenation (dotted line, upper part) and for reduction of PAP (dotted line, lower part) are indicated on the x-axis. Note the different ED_{50} for P_{aO_2} and PAP, and the diminished effect of 100 ppm NO compared to 1 ppm and/or 10 ppm NO on the arterial oxygenation. (Reprinted from Reference 42, with permission.)

was positive. We tested the dose response of INO on selective pulmonary vasodilation in patients with severe ARDS, using INO concentrations ranging between 10 parts per billion (ppb) and 100 ppm, and found that an improvement of systemic oxygenation by NO can be achieved with much lower doses of NO than have been used in previous studies. We found that the median effective dose (ED_{50}) for increasing oxygenation was approximately 0.1 ppm. In addition, the best dose for improved oxygenation is different from that for optimal reduction of pulmonary resistance ($ED_{50} > 2$ ppm) (Fig. 3).[42] The optimal improvement of systemic oxygenation is usually obtained with 10 ppm NO; higher doses of NO can reverse the beneficial effect. In some cases, however, ARDS patients have had an impressive effect with INO, demonstrating the best systemic oxygenation with 1 ppm NO, whereas higher doses (eg, 100 ppm) showed effects similar to systemic vasodilators (ie, deteriorated systemic oxygenation due to increased intrapulmonary right-to-left shunt areas). By contrast, pulmonary resistance decreased in direct proportion to the INO concentration (ie, pulmonary resistance continued to decrease as INO concentration increased).

The response to INO varied both between patients and in individual patients during INO treatment. Some patients were nonresponders (ie, they showed little or no improvement from INO treatment). Among the responders, the optimal INO concentration to enhance systemic oxygenation was from 0.5 to 100 ppm. In some patients, long-term INO in the range of 0.06 ppm to 0.25 ppm (after the individual dose response study) corresponded to as much as 2 weeks of improved systemic oxygenation.[18] The latter concentration range is similar to the endogenous NO concentration produced in the upper airways and autoinhaled during normal ventilation.[43,44] Thus, low-dose INO might be considered a replacement therapy, since mechanical ventilation disallows the natural autoinhalation of endogenous NO from the upper airways.

We also performed a prospective, randomized, placebo-controlled single-center clinical trial on the time-dependent dose response characteristics of long-term NO inhalation in patients with severe ARDS. The patients were evaluated according to a standard protocol. At the time of inclusion, none of the patients received venovenous extracorporeal membrane oxygenation. After an initial dose response analysis of INO, using inhalation concentrations ranging from 0.01 up to 100 ppm NO, patients were randomized. The INO group received continuous administration of 10 ppm NO, regardless of their response with respect to systemic oxygenation or pulmonary hypertension. Every day, the effect of the NO inhalation was controlled (on-off-on tests). After 48 hours, a 2nd dose response curve was charted, as well as afterwards in a 48-hour time course. NO inhalation in the NO group was continued until the F_{IO_2} could be reduced to 0.4 for keeping the P_{aO_2}/F_{IO_2} higher than 60 mm Hg under pressure-controlled ventilation with a maximum PEEP of 10 cm H_2O.

A statistical analysis of 40 patients (20 patients receiving INO and 20 patients not receiving INO) revealed that both groups had no significant differences at time of inclusion in the study with respect to epidemiology, including the initial catastrophic event, hemodynamics, gas exchange, and other parameters. The initial dose response curves for systemic oxygenation and reduction of pulmonary hypertension were identical, demonstrating a peak effect for oxygenation at 10 ppm NO, as described above.[42] In the subsequent days, there was an overall tendency towards improved oxygenation and decreased pulmonary hypertension. Interestingly, the data for PAP after 48 hours indicated that a sudden shut-off of NO resulted in a higher PAP baseline compared to the control group. That is, that the patients were sensitized for INO. Furthermore, the NO effect in the control group was no longer significant. This suggests that NO treatment might not really be beneficial, since the PAP in the NO group during NO inhalation was not significantly different from the baseline PAP in the control group.

Similar data were found for the systemic oxygenation. Compared to the control group, the initial reduction of F_{IO_2} in the NO group, due to the positive effect of INO on systemic oxygenation, was only significant at the day of inclusion. This agrees with results from other published randomized studies.[38–41] Thus, we doubt the assertion that INO makes it possible to reduce aggressive ventilation. Further studies are needed to clarify if this phenomenon is due to inhibition of endogenous NO synthesis, or to an interaction of high oxygen concentrations with NO, possibly inducing toxic metabolites such as NO_2 or peroxynitrite. The outcome in terms of survival, intensive care unit stay, or ventilation days (whether for all patients or only for those who survived) was identical in both groups. Patients from the NO group, however, required significantly less venovenous extracorporeal membrane oxygenation than control patients. The total number of patients is very small, but these data indicate that INO might be considered as a bridging therapy for severe hypoxemia in lieu of more invasive and expensive strategies.

Another interesting finding of the latter study was that the time course of dose response curves from the patients differed depending on the initial randomization. Control patients demonstrated similar dose response characteristics over time, with a peak effect of INO on systemic oxygenation at 10 ppm NO regardless of when the analysis was performed. These findings are in accord with results from former studies.[42] Patients from the INO group, however, had a shift to the left of the dose response curve for systemic oxygenation within 96 hours. After this time, the peak for oxygenation was found at 1 ppm NO (ie, continuous inhalation of 10 ppm NO sensitized these patients). This might be important because the INO concentration of 10 ppm was no longer in the ideal range, compared to the initial data, and, in some patients, led to a decrease of P_{aO_2}! This may explain why, in previous studies, improvement of oxygenation was only seen during the first 24 hours of INO, and suggests that a programmed reduction of INO concentration might be indicated.

Theories of NO Transport

In probably more than 80% of patients with ARDS, (1) lower doses of INO improve systemic oxygenation, (2) higher doses, in contrast, lower the arterial oxygen content, and (3) improvement of systemic oxygenation and reduction of pulmonary artery pressure are not correlated during NO dose response studies.[42] These observations support two hypotheses:

(1) Diffusion theory. NO is highly lipophilic, with a low molecular weight, and quickly diffuses into tissue, reaching a balance between the rate of diffusion and the rate of NO oxidation or binding to targets. Inhaling low doses of NO probably induces a diffusion only into the capillaries of the ventilated alveoli. Thus, with lower NO doses there is a more or less strictly selective vasodilation in ventilated areas of the pulmonary vasculature, which reduces intrapulmonary shunt areas and thereby increases systemic oxygenation. With higher NO doses, however, diffusion of NO through the lung tissue also reaches nonventilated areas (ie, shunt areas); this still provides selective pulmonary vasodilation, but reverses the beneficial effect on oxygenation by causing vasodilation of shunt vessels.

(2) Transport theory. This theory is based on the finding that INO binds to albumin and hemoglobin and in this way can be transported through the pulmonary vessels and thereby affect areas outside the lung.[45] The vascular system of the lung, in contrast to other organs like the liver, is strictly dichotomous. That is, from the pulmonary artery up to the final capillaries, each vessel divides progressively into smaller vessels, without any transverse connections between vessels. After the capillary system, 2 vessels always re-join into a larger one, until the pulmonary veins are reached. This means that vessels of shunt (non-ventilated) areas and of areas with ideal ventilation/perfusion ratios are finally united in the pulmonary venous system. Thus, if NO is inhaled in low doses, it causes a low local concentration, which acts on the vascular smooth muscles of the vessel. Since the concentration is low, diffusion of INO into the intravascular space and binding to albumin and/or hemoglobin can not occur before the venous vessel is rejoined with a shunt vessel. Thus vasodilation and increased flow occur only in the ventilated area. With high doses of NO, intracapillary concentrations increase and NO is transported, which can result in a decreased "afterload" for both ventilated and nonventilated areas, since the NO is active after the vessels rejoin.

Both of the latter theories are speculative. The diffusion theory might be favored because NO is believed to act on the vascular smooth muscle cells of the capillary before it is resorbed into the intravascular space. The remarkable reduction of pulmonary artery pressure by NO may also be an argument for the diffusion theory because the alveolar capillaries have few or no smooth muscle cells (and therefore very little effect on pulmonary resistance), and the arteries and arterioles are believed to be a regulating factor for pulmonary vascular resistance. How can NO get to the arteries if not by diffusion? If, however, NO has to diffuse through the pulmonary tissue to have an effect, how can we explain the selectivity for ventilated areas with low doses of NO? This favors the transport theory. Furthermore, studies by Jia et al revealed that NO binding to hemoglobin is not selective to the heme group leading to nitrosyl-hemoglobin, but also involves cystein domains, preferably from oxygenated hemoglobin forming S-nitrosohemoglobin.[45] After reduction of oxygenated hemoglobin in the systemic capillaries, NO's affinity for hemoglobin is reduced, which leads to detachment of NO and thereby to peripheral vasodilation.[46] These findings by Stamler et al contradict the hypothesis that NO is neutralized by hemoglobin and that INO therefore has only local, intrapulmonary effects. Indeed, while INO seems to be taken up by hemoglobin and albumin in the lung, it is probably transported to the systemic periphery, liberated because of the oxygen gradient, and causes vasodilation in small arteries. These results are important to understanding the dose-dependent, local, and systemic effects of NO and thus merit further research on the clinical use of INO.

Summary

INO treatment for severe ARDS and other forms of pulmonary hypertension is a new and encouraging concept. However, there is no evidence as yet that INO improves outcomes of these conditions. As well, specific effects in individuals are not predictable, so experimentation with varying concentrations of INO for individual patients is indicated. However, it is difficult to know whether to target optimal systemic oxygenation, or to seek maximum reduction of pulmonary resistance, or if something in between is the optimal treatment for a particular patient. This uncertainty and the variable effects of INO in ARDS patients make it very difficult to perform the sort of prospective, randomized controlled studies that are needed to demonstrate whether INO can help lower the mortality of ARDS.

Very low doses of NO (similar to environmental concentrations) have shown beneficial effects in ARDS patients, and so far no significant adverse effects have been observed. However, further research on adverse effects of INO is warranted, especially with regard to immunological and neurological functions, because NO is a complex biological mediator. Because INO's adverse effects have not been fully determined, INO should only be administered under clear and rigorous protocols. Recommendations for basic requirements of these protocols include: (1) ethical requirements (Declaration of Helsinki, Good Clinical Practice, approval of the hospital's ethical committee, insurance for the patient, informed consent from a relative), (2) evaluation of patients (defined inclusion criteria, repeated dose response studies, identification of responders and non-responders, strategy of dosing of INO over time, primary and secondary targets), (3) NO/NO_2-measuring systems (continuous measurement of NO and NO_2 by electrochemical sensors during long-term use, chemiluminescence analyzers for dose response curves), (4) set procedures for storage of NO gas (environmental safety), and (5) standardized systems for administering NO (including feedback controls and alarm systems; no home-made systems). INO should not yet be considered a standard therapy!

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Discussion

Branson: That was an excellent presentation. I have a couple of comments and a couple of questions. The first comment is that the data by Dellinger from the randomized trial[1] shows that P_{aO_2} becomes equal in both groups after the first day, but F_{IO_2} and mean airway pressure are reduced in the group receiving NO, which is something that I don't think came out in your data. Is it appropriate, and how do you determine dose response over such a short period of time—in 30 seconds—and measure the P_{aO_2}? What's the method by which you do that?

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Gerlach: It was 30 minutes.

Branson: Oh, I thought you said 30 seconds, and was thinking that effect was so short. What about rebound? What causes rebound, what causes that fall, and how can we tell when the patient's been on NO for 2 days or 5 days or 10 days when they're no longer responding to NO?

Gerlach: This is not a rebound phenomenon, but a phenomenon of decrease in oxygenation with increasing doses of NO. So, maybe I said something confusing, but it was 30 minutes with increasing doses, and you saw this decrease of the P_{aO_2} during the increase of the NO concentration. This is different from a rebound phenomenon, and I would call it an overdosing of NO. As I said, the declarations for this phenomenon are not done. The one theory is that NO acts locally and diffuses into the smooth muscle cells of the ventilated areas, thus providing a simple dose-dependent diffusion effect due to a gradient from the inhaled vessel away until you reach nonventilated areas. This induces a stealing effect similar to patients who get intravenous vasodilators. The other theory is that the INO gets reabsorbed by hemoglobin and is transported away. This is something which might be discussed in the future because, as I said in the discussions previously, it was shown that INO is acting outside the lung. The resistance vessels of the lung are before the alveoli. Here is the effect. It can be shown by some studies. I know of one study[1] from Freiburg, Germany, that showed that lowering the pulmonary vascular resistance in the lung by inhaling NO is an effect of the so-called resistance vessels prior to the alveoli, which means it has followed one circuit through the body, at least. These 2 theories are discussed at the moment. The reason for the rebound phenomenon was investigated in several in vitro studies and in animals, and showed that the INO is reducing the NOS activity in the lung. This might be the reason why you might have an anti-inflammatory effect and an anti-NO synthesis effect from INO.

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Branson: From a practical standpoint, how do you determine what the best dose is on a given day and when to discontinue it? Do you have any recommendation?

Gerlach: No. In Germany, we are very strict. We say it's an experimental phase for the evaluation of NO, and we do not give any recommendations. It is limited, at least in Germany and in Europe, to studies and to special groups. Meanwhile, in Sweden and now in Germany, the government made very strict reduction of the use of NO because of data from case reports about cerebral bleedings. They say they will not be ready to allow the use of NO as a drug for everybody.

Bigatello: This was a very interesting talk. I am particularly intrigued by your data on the shift to the left of the dose-response curve during chronic NO inhalation. Is that right?

Gerlach: In the NO group. Yes. Correct.

Bigatello: I need a little more explanation on how you did it, because to me that would have some quite interesting clinical implications. Could you just repeat to me how you did the dose-response curves every day? Did you stop the NO and repeat the dose-response?

Gerlach: No. When we do dose-response curves, we start with zero and then we start with 0.01, zero, 0.1, zero, 1, zero, 10, zero, etc.

Bigatello: Right. But then you have a patient who is on NO. I can understand your dose response at the beginning when the patient is not receiving anything. But the next day, is the patient still on NO, or. . . ?

Gerlach: If he is in the NO group.

Bigatello: Right, so how do you do the dose-response when the patient is still on NO?

Gerlach: We put it off, for instance . . .

Bigatello: All right; you put it off for a while, and then you repeat the dose-response.

Gerlach: Yes.

Stewart: When you stop it, don't you get rebound?

Gerlach: Sure we get rebound phenomenon, similar to during weaning from NO. Sometimes we have to lower the concentration down to 50 ppb, and then we put the NO off and the patients have bad oxygenation and bad pulmonary artery pressure, but, in our experience, this is in fact between 1 and 4 hours. They then are back on baseline.

Stewart: OK. You said the data were from 1998. Where are these data published? Or are they published?

Gerlach: No, they are not yet.

Bigatello: Now, you have your patient on NO who you think is becoming more sensitive to low doses of NO, that he may start not benefiting, or even be damaged by higher doses, in terms of P_{aO_2}. So your 20 ppm dose at the beginning may 5 days later decrease the P_{aO_2}, or work less well than before, correct?

Gerlach: Sometimes it doesn't even work any more.

Bigatello: So would it be fair to speculate that maybe one of the reasons why we see the effect of NO wear off over time is that 5 days later 10 ppm may be too much, and if we would give 1 ppm it will work better?

Gerlach: Yes, of course. That's the conclusion.

Bigatello: That's a pretty big conclusion!

Gerlach: That's the point of the study. We did not believe the data before the end of the study, because we said "OK, let's do an intent-to-treat study. The patients get 10 ppm NO. We don't care about the dose-responses and we just watch them." If we now do the next study, we would change the protocol. We'd say "Don't give 10 ppm anymore: go to the optimum dose from now on."

Bigatello: You haven't done it yet, though?

Gerlach: No.

Channick: Have you done this in reverse where you started at 20 ppm and you gradually worked the dose down and see oxygenation improve? Or do you always go to zero and go back up again?

Gerlach: We always go to zero between the doses.

Channick: The patient's on 20 ppm for a few days. You then start dropping the dose and see improvement in oxygenation, as opposed to going back to zero and then going up again?

Gerlach: No. Our protocol was based on a constant dose of 10 ppm. However, just over the days that we treated the patients, we did not reduce the dose for treatment; we only changed the dose for the dose-response analysis. One of the main conclusions was that you have to reduce the concentrations, probably very quickly after 12 hours, and even lower after 24 hours.

Hurford: The 3 dose-responses you showed us were done over what time periods?

Gerlach: The whole time was about 2 hours.

Hurford: Right. But were they done on day 1, day 2, day 3. . . ?

Gerlach: Two, 48 and 96 hours. Day zero, day 2, and day 4.

Hurford: OK. Just a follow-up question. What do you do about ambient levels of NO that are in the air? In Paris they can be very high, 500 ppb. What are they in Berlin? And how do you account for this?

Gerlach: Ambient NO concentrations in Berlin are between very low ones and about 200 ppb. But we definitely had days when the ambient concentration was higher than the NO dose we were currently administering to the patient. I remember one child when we used 60 ppb and we could not get him off the 60 ppb. Somebody said "Just extubate him because he is continuously breathing, and the ambient NO concentration is 85 ppb."

Hess: I wonder if you could speculate a bit about whether INO with ARDS could have benefit even though there is not a response as far as oxygenation? You mentioned a little about the platelet effects. What about anti-inflammatory effects, for example?

Gerlach: There are a lot of experiments from different groups about this so-called anti-inflammatory response. There are other studies on the induction of programmed cell death, the so-called apoptosis that seems to be very important because the reconfirmation of the lung during the late phase of ARDS is dependent on apoptosis. There are different theories, if INO might be beneficial because you get a greater induction of cell death inside the lung because the apoptosis is the reason for the fact that the fibrinocytes are getting grabbed out of the alveoli. So this is one reason for the anti-inflammatory response. I think the balance between NO, oxygen radicals, and peroxynitrite is a very sensitive balance. Studies by Murakami,[1] for instance, showed that in a model involving ARDS in rats, 30 parts per million reduces the inflammatory response. If you use more, you have even worse, and more lipid peroxidation, and you have a pro-inflammatory effect, probably by the production of peroxynitrite. We did some in vitro experiments with monocytes looking for the expression of tissue effect and we saw the same. You can follow it down to the molecular biology and see that low doses of NO are able to block the production and expression of tissue factor.[2] Higher doses of NO probably convert to peroxynitrite, which influences tyrosine residues and induces an inflammatory response. That's the reason why on the slide it said anti-inflammatory and pro-inflammatory effects. To my knowledge, so far there are no data showing a beneficial effect. Payen[3] showed that you have less neutrophils in the bronchoalveolar lavage, but who knows if it's good or bad? This is part of the host's response. If we block the host's response, we do not know if this is beneficial or not.

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Pearl: Do you have comments on the efficacy of NO in early versus later ARDS, and on pulmonary versus extra-pulmonary etiologies of ARDS?

Gerlach: No. The patients we put on NO were all patients from outside our hospital, and we included these patients very quickly, within 48 hours. Some of these patients had a very long history, up to 3 weeks of ARDS. The data are too few, with too few patients to make a stratification. In our study, the mean time of ICU treatment the day before they get NO was the same in both groups. What we can see is that there obviously seem to be more nonresponsive patients if they have viral pneumonia (for instance, severe pneumonia with varicella, typically a very homogenous disease). In these patients you see little or no effect from NO. Some data from Rouby[1] from Paris showed that there is a difference if you see these inflamed lungs in contrast to a polytrauma patient. The more inhomogenous the lung is, the more effective is NO.

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Branson: I just want to ask one more question. My impression of the Siemens delivery device is that it's very, very accurate, but I'm always troubled that it monitors the gas on the expired side. Isn't the measured NO then affected by NO uptake, and how reliable, or how sure are you that that's the dose when you're giving 0.1 ppm or 0.01 ppm? What dose is the patient really getting?

Gerlach: You can apply the measurement where you want. An electrochemical cell is built into the machine, usually on the expiratory side. The data I showed were from the inspiratory limb where we used our own equipment with an external chemiluminometer.

Bigatello: Did you also measure your dose-response with another analyzer like a rapid response analyzer? What I'm getting at is that maybe your absolute numbers measured that way are not perfect, although I don't care too much. I'm still very impressed by the fact that your dose-response moves. With a Sievers analyzer, you may see a more precise dosing. But I don't think that takes anything away from your data, because it's the movement of the dose-response that is interesting to me.

Gerlach: Of course, you have some patients who do not react like this. This was the mean of 20 patients inside the NO group. We use an external device for all these dose-response studies, and not the built-in device of the machine. Using a chemiluminometer we're going down in concentrations. We need a fast response device and a machine that is measuring down to 5 parts per trillion. Response time is 10 milliseconds. I will show this in my talk about exhaled NO tomorrow. I have some slides from this machine. And the third point, of course, is that the data I presented were from the NO group, and I didn't show the slides from the non-NO group, which had more or less the same dose response over time.

Hurford: I have one question that's a problem that I've been trying to explain to my surgeons, much to their regret. In our series we have data very much like everybody else's, where overall we haven't affected mortality rate or anything else as far as measurable outcome data goes. Except my thoracic surgeons didn't believe me, so I gave them my data, and they analyzed their patients with postpneumonectomy ARDS. They came back to me and showed a persistent improvement in P_{aO_2}, F_{IO_2}, and, at least by historical data, a decrease in mortality rate from 80% to 30% in that patient population. Now, how do I explain to them there's no effect?

Gerlach: You can only prove this with a controlled study. I wouldn't say the data are wrong. I think we'll hear something from lung transplantation where you can see an NO effect on ischemia-reperfusion injury. You probably do have an effect which is based on a cyclic GMP-independent pathway and has nothing to do with vasodilation. A transplant unit in Hannover, Germany, showed that host transplant edema of lung transplant is tremendously decreased by INO. But you have to be careful. You have to inhale it 12 hours and then pull the brake. I saw some cases where INO was administered 12–24 hours, and suddenly patients reached a condition like ARDS and there was no improvement. I think it is possible to limit this technique in terms of dosing and timing. All together, I would be very cautious. I hate to say it's effective or that it's not effective.

Hurford: I think that's our challenge now, to try to sort this all out.

Inhaled Nitric Oxide for Cardiac Disease

George F Rich MD PhD, Stuart M Lowson MD, and Victor C Baum MD

Pulmonary Hypertension and Right Ventricular Failure
  Physiology and Pharmacology
  Traditional Management of Pulmonary Hypertension
Theoretical Advantages of INO
INO for Mitral Valve Surgery
INO for Cardiac Transplantation Surgery
INO for Cardiac Failure Requiring Left Ventricular Assist Device
INO and Right Ventricular Function
INO and Left Ventricular Dysfunction
INO and Pediatric Heart Surgery
  Physiology and Pharmacology
  Perioperative Use of INO for Pediatric Patients
  Safety Issues in Pediatric Patients
Practical Operating Room Application
Summary

[Respir Care 1999;44(2):196–202] *Key words: nitric oxide, NO, cardiac disease, cardiac transplant, pulmonary hypertension, cardiac failure, ventricular assist device.*

Pulmonary Hypertension and Right Ventricular Failure

Physiology and Pharmacology

Mitral valve disease and other cardiac diseases can result in elevated left atrial pressure, which can cause a passive increase in pulmonary venous pressure, and reactive pulmonary vasoconstriction. Eventually, morphologic changes in the pulmonary vasculature, including increased musculature and reduction in cross sectional area, result in increased pulmonary vascular resistance (PVR). Cardiac conditions can exacerbate pre-existing hypoxic or obliterative pulmonary disease, which also elevates PVR. In children, increased pulmonary muscularity occurs when pulmonary blood flow is increased by ventricular septal defects, atrioventricular septal defects, and aortic valveanomalies. The pulmonary circulation of infants is often highly reactive or responsive to neural or humoral factors that cause pulmonary vasoconstriction. Early in the disease states that result in pulmonary hypertension, the elevated PVR is pharmacologically reversible. As the wall of the pulmonary vessels thickens, progressive obliterative pulmonary changes occur, and pharmacological therapy can become ineffective.

Pulmonary hypertension can have a significant impact on right ventricle (RV) function. The primary effect is increased RV afterload, as measured by increased PVR. The RV is normally a thin-walled structure that is highly distensible. Unlike the left ventricle (LV), the RV is unable to withstand large increases in afterload. This is particularly true after acute increases in PVR, when even small increases in PVR can lead to reductions in RV stroke volume and cardiac output (C.O.).

Increased PVR and poor RV function can also contribute to decreased C.O. and systemic hypotension by impacting LV function. A dilated RV and right atrium resulting from pulmonary hypertension can shift the intraventricular septum and compress the left atrium and ventricle, resulting in decreased LV filling and decreased LV end diastolic volume.

Increased PVR can aggravate RV failure and prevent recovery of RV function after cardiopulmonary bypass

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(CPB). In addition to pre-existing disease states, RV dysfunction after CPB can result from inadequate preservation of the RV during CPB, production of pulmonary vasoconstrictors such as thromboxane A_2 resulting from platelet and leukocyte aggregation, or decreased endogenous pulmonary vasodilators such as nitric oxide (NO).

Traditional Management of Pulmonary Hypertension

Traditional management of pulmonary hypertension includes treatment of both passive and active factors that influence PVR. These include optimization of arterial blood gases, ventilation, blood volume, temperature, and level of anesthesia. These have been reviewed in detail[1,2] and will not be discussed further herein.

Pharmacologically, pulmonary hypertension has traditionally been treated by administration of nitroglycerin or sodium nitroprusside. Although both of these decrease PVR, they can also result in systemic hypotension. Additional agents that have been used, with variable success, include hydralazine, nifedipine, and α-adrenergic antagonist agents such as tolazoline and phentolamine. Prostaglandin E_1 and prostacyclin are 2 potent pulmonary vasodilators. Low doses of these agents are relatively specific to the pulmonary circulation, but at higher doses produce substantial systemic vasodilation. The phosphodiesterase inhibitors, which combine both positive inotropic and vasodilating effects, are also potentially useful in treating pulmonary hypertension, but neither is specific to the pulmonary circulation. Isoproterenol also combines positive inotropic effects with pulmonary vasodilation, but also causes tachycardia and systemic vasodilation, which significantly limits the usefulness of this agent.

Theoretical Advantages of INO

The specificity of inhaled NO (INO) for the pulmonary circulation is well-described. INO causes cyclic guanidine monophosphate-mediated pulmonary vasodilation by diffusing from the alveoli into the pulmonary vascular smooth muscle. Systemic vasodilation is prevented by the rapid inactivation of NO by hemoglobin as INO enters the circulation.

Ideally, agents that treat pulmonary hypertension would have no effect on the systemic circulation. This is particularly important when pulmonary hypertension is combined with RV failure. Coronary perfusion pressure is dependent on systemic pressure, and a decrease in mean systemic arterial pressure can decrease coronary blood flow to an already failing RV. All intravenous medications cause some degree of systemic vasodilation, whereas INO is selective for pulmonary vasodilation. INO apparently has no effect on heart rate.

INO for Mitral Valve Surgery

The potential value for INO to acutely decrease PVR has been observed in patients before and after mitral valve replacement[3–5] and coronary artery bypass graft surgery.[6] Most studies tested the hemodynamic response to a single dose of INO at 20–40 parts per million (ppm), and observed a reduction in PVR but no systemic hemodynamic changes. Lindberg evaluated a dose response to INO from 2 to 25 ppm, and found that the full hemodynamic response was observed at 2 ppm.[6] Our group found that the magnitude of the reduction in PVR in response to INO was proportional to the baseline PVR.[3] INO has no effect in patients without pulmonary hypertension.

None of the patients in these studies had sufficient pulmonary hypertension to cause RV failure. Although the effect on RV ejection fraction was not determined, INO did not cause an increase in C.O. While reduction in PVR is common with INO in patients with mitral valve disease, clinical benefit is unlikely unless PVR is a limiting factor for RV dysfunction and C.O. Patients with mitral valve disease can have significant pulmonary hypertension, but surgical correction usually results in a dramatic and immediate decrease in PVR. The incidence of RV failure in conjunction with pulmonary hypertension during cardiac surgery is also relatively low compared to LV failure, especially if treatment is rendered before the disease becomes severe. Although there are no long-term studies of INO in these patient populations, INO is likely to be beneficial in patients who do have difficulty with discontinuation from CPB secondary to RV failure and pulmonary hypertension.

INO for Cardiac Transplantation Surgery

Normally the RV is accustomed to a low afterload, and a significant acute increase in PVR can cause RV failure. This frequently occurs in patients undergoing cardiac transplantation (CT). The recipient commonly has an elevated PVR as a result of longstanding congestive heart failure (CHF). When the donor RV, which is accustomed to a normal PVR, is acutely exposed to an increased afterload, the RV might fail. Data from the Registry of the International Society for Heart and Lung Transplantation indicate that RV dysfunction accounts for approximately 50% of all cardiac complications and 19% of all early deaths following CT.[7]

An elevated PVR of greater than 400 dyn·s·cm^{-5} is generally considered a contraindication to CT. INO can be useful to evaluate the dynamic response of pulmonary vasculature prior to CT in order to determine whether the pulmonary hypertension is fixed or if there is a reversible component.[8] Studies have suggested that INO is superior to other agents in predicting acute reversibility of PVR.[8]

Following transplantation, RV adaptation to the new hemodynamic conditions usually occurs over a 48 hour period,[9] and INO might reduce PVR to an acceptable level until the adaptation is complete. One case report showed that a patient with severe pulmonary hypertension was supported with nasal NO (50 ± 23 ppm) until CT.[10]

Post-transplantation, INO was found to be effective in a dog transplantation model involving monocrotaline-induced pulmonary hypertension in the recipient.[11] In case reports and studies involving patients with pulmonary hypertension post CT, Kieler-Jensen showed that 20 ppm INO acutely decreased PVR from 252 ± 30 $dyn{\cdot}s{\cdot}cm^{-5}$ to 166 ± 16 $dyn{\cdot}s{\cdot}cm^{-5}$, while producing a modest increase in C.O., from 5.4 ± 0.7 to 6.0 ± 0.6 L/min.[12] Right ventricular ejection fraction was not significantly increased (24% vs 27%). None of the patients received INO long-term. A case report from Girard found that 25 ppm INO acutely decreased PVR, from 400 $dyn{\cdot}s{\cdot}cm^{-5}$ to 234 $dyn{\cdot}s{\cdot}cm^{-5}$, while producing a large increase in C.O., from 2.7 $L/min/m^2$ to 3.6 $L/min/m^2$, which was observed while NO was continued for 48 hours.[13] In that case report, the initial pulmonary hypertension was much greater than that in Keiler-Jensen's report, which probably explains the relatively greater hemodynamic effect of INO. INO is of potential benefit in pulmonary hypertension patients if there is accompanying RV failure, but there have been no long-term studies to determine the influence on morbidity or mortality.

INO for Cardiac Failure Requiring Left Ventricular Assist Device

Patients who are not weanable from CPB because of ventricular failure, and patients with advanced CHF, might require a left ventricular assist device (LVAD) in order to maintain satisfactory C.O. An elevated PVR can limit blood flow to the left atrium and decrease LVAD flow. Furthermore, 25–40% of patients requiring an LVAD have or acquire RV failure.[14] Management of RV failure in LVAD recipients includes ensuring adequate RV preload, maintaining sinus rhythm, and administering intravenous vasodilators. However, the utility of intravenous vasodilators is limited by the systemic vasodilation they cause, which can decrease coronary artery perfusion pressure and further compromise RV function. Right ventricular assist devices are occasionally required to improve C.O. but their insertion is associated with increased complication rates.

Argenziano studied patients with heart failure post-CPB who required LVAD insertion and who had pulmonary hypertension with limited LVAD flow.[15] INO resulted in a clinically significant decrease in mean pulmonary artery pressure (PAP), from 35 ± 6 mm Hg to 24 ± 4 mm Hg, and an increase in LVAD flow, from 1.9 ± 0.2 L/min to 2.7 ± 0.3 L/min. All patients were successfully weaned from INO in less than a week. Wagner investigated the effect of 0–40 ppm INO in patients with end-stage CHF who developed RV dysfunction following LVAD insertion.[16] INO caused a significant decrease in PAP (at doses ≥ 10 ppm INO) and PVR (at doses ≥ 15 ppm INO), while cardiac index (CI) increased from 2.0 ± 0.4 $L/min/m^2$ to 2.7 ± 0.4 $L/min/m^2$ (at doses ≥ 20 ppm). Over the course of 2 to 8 days, the RV ejection fraction increased from 24 ± 7% to 44 ± 7%. These studies indicate the PVR is decreased and LVAD flow is increased. RV function might also be enhanced. Although it is likely that chronic INO therapy is beneficial in these patients, there have been no controlled studies that demonstrate a decreased need for right ventricular assist devices or enhanced RV recovery.

INO and Right Ventricular Function

Pulmonary hypertension is present in the majority of patients with acute respiratory distress syndrome, but the RV is usually able to compensate for the increased PVR, because the increase occurs gradually. Two studies in patients with acute respiratory distress syndrome have demonstrated that 5–18 ppm INO decreases PVR and causes a small increase (3–10%) in RV ejection fraction.[17,18] However, none of the patients were in RV failure, and INO therapy was not associated with an increase in C.O. Benzing suggested in a case report that 40 ppm INO might make a clinically significant difference if RV failure occurs with acute respiratory distress syndrome.[19] In that case report, the central venous pressure was decreased from 29 mm Hg to 24 mm Hg, and PVR was decreased from 322 $dyn{\cdot}s{\cdot}cm^{-5}$ to 164 $dyn{\cdot}s{\cdot}cm^{-5}$, while the C.O. was increased by 32%, from 5.2 L/min to 7.3 L/min. We recently managed a patient with severe acute lung injury requiring an adult oscillator ventilator to achieve adequate gas exchange. The patient gradually developed pulmonary hypertension, with a PAP of 70/40 mm Hg, associated with a decreased cardiac index and mixed venous oxygen saturations of less than 50%. INO at 10 ppm produced a large increase in CI, from 2.0 $L/min/m^2$ to 4.4 $L/min/m^2$, and an increase in mixed venous oxygen saturation, from 45% to 70%. Although there was a significant decrease in PVR, there was no change in PAP, probably because the increased pulmonary blood flow compensated for the vasodilation. The concentration of INO was titrated against the CI rather than the PAP, and we were able to decrease the concentration of INO to less than 5 ppm and still achieve the hemodynamic effect.

These studies indicate that INO acutely decreases PVR, while having variable effects on RV function and C.O. The greatest beneficial effect is likely to be in patients with RV dysfunction and greater degrees of pulmonary hypertension. Case reports and small studies suggest that

INO can be beneficial, but outcome studies on RV function with chronic INO have not yet been reported.

INO and Left Ventricular Dysfunction

In patients with LV failure, there have been a number of studies that indicate that INO can cause an increase in left heart filling pressure.[8,20–22] Loh examined the effects of 80 ppm INO in patients with New York Heart Association class III and IV CHF dysfunction.[20] INO caused a 31 ± 7% decrease in PVR, from 226 ± 30 dyn·s·cm^{-5} to 119 ± 13 dyn·s·cm^{-5}, but neither PAP (35 ± 4 mm Hg) nor CI (2.3 L/min/m^2) changed. The decrease in PVR was entirely due to a decrease in the transpulmonary artery pressure gradient (PAP minus pulmonary artery wedge pressure [PAWP]), which resulted from a 23% increase in PAWP (25 ± 3 mm Hg to 31 ± 4 mm Hg). Patients with more severe LV dysfunction (as evidenced by higher left heart filling pressures, lower stroke volume, and larger LV cavity size) showed the greatest increase in PAWP. Adatia found that those patients with the highest baseline PAWP (27 ± 4 mm Hg) demonstrated the greatest decrease in PVR in response to INO (at 80 ppm), but also had the greatest increase in PAWP.[21] Likewise, Semigran found that in patients with LV dysfunction, there was a dose-dependent increase in PAWP, with 80 ppm INO causing a greater increase than 20 ppm or 40 ppm.[22]

The most likely explanation for the increase in PAWP (in patients with severe LV failure, in response to INO) is that the selective pulmonary vasodilation acutely augments venous return to the LV. For a given PAP, a decrease in PVR results in an increase in driving force for LV filling. Since the failing LV operates on the steep portion of the diastolic pressure/volume curve, a small increase in LV volume can result in a substantial increase in PAWP. The increased left heart filling pressure might therefore result in worsening cardiac failure and acute pulmonary edema.[23] This has been proposed in a theoretical model of cardiac failure[24] and is supported by one clinical study in patients with LVADs.[25] Hare studied the cause of increased left heart filling pressure in response to INO in patients with end-stage CHF receiving circulatory assistance with the Heartmate IP 1000 LVAD (Thermocardiosystems Inc, Woburn, MA).[25] The response to INO was examined with the device set to deliver either a fixed or variable output in response to changes in filling pressures. INO decreased PVR with both pump settings. LV filling pressure increased with the fixed output mode but remained unchanged with the variable mode.

It is also possible that INO exerts a negative inotropic effect on the myocardium. Evidence from both animal models and patients suggests that endogenous myocardial NO exerts a negative inotropic effect.[26,27] Endogenous NO inhibits β-adrenergic inotropic responses,[28] and inhibition of cardiac NO production increases the positive inotropic response to β-adrenergic receptor stimulation in patients with CHF, but not in control subjects with normal LV function.[29] Increased inducible nitric oxide synthase within endothelial cells and cardiac myocytes is associated with reduced myocardial inotropic ability in animal models.[30] However, for INO to exert a negative inotropic effect on the LV it would have to reach the myocardium, and it has been demonstrated that INO is immediately inactivated once it crosses into the pulmonary circulation. A negative inotropic effect of INO has not been observed in animal models of LV failure.[31] Furthermore, in patients with LV failure, Loh found that INO had no effect on LV peak dp/dt (a sensitive measure of the contractile state), despite increasing left ventricular filling pressures.[20] Similarly, Hayward found that 20 ppm INO had no effect on steady state LV pressures, volumes, or contractility in patients with normal LV function.[32]

When RV and LV failure are both present, INO has been observed to improve exercise capacity. Koelling performed exercise testing on patients with NYHA class III CHF before and after administering 40 ppm INO,[33] and found that none of the differences in primary exercise end-points for the group as a whole were significant. However, on subgroup analysis, oxygen consumption at the anaerobic threshold significantly improved in response to INO in patients with increased PAP (> 30 mm Hg) and patients with increased left ventricular end-diastolic volume index. INO significantly increased the peak work load with exercise in patients with resting RV ejection fraction < 0.35. This study suggests that patients with pulmonary hypertension in conjunction with decreased RV ejection fraction are likely to benefit from INO therapy and supports the hypothesis that physical activity of patients with severe CHF is limited by pulmonary hypertension and/or RV dysfunction.

The above-discussed studies suggest caution in administering INO to patients with LV dysfunction. Because INO can cause acute pulmonary edema in these patients,[23] INO can be contraindicated in patients with LV dysfunction alone. Patients with biventricular failure might benefit from INO if elevated PVR is a limiting hemodynamic factor, but careful patient monitoring is necessary.

INO and Pediatric Heart Surgery

Physiology and Pharmacology

The same types of lesions which can result in pulmonary hypertension in adults, such as mitral stenosis, can occur in infancy and childhood.[34] However, there are additional factors that make pulmonary hypertension during and after cardiac surgery more likely in children. Children can also be more sensitive than adults to elevations in

PAP. Pulmonary vasculature in infants is often very labile, which can be responsible, in extreme instances, for persistent pulmonary hypertension of the newborn. Unlike adults, many children who require cardiac surgery require it because of congenital cardiac defects involving intracardiac shunts. Left to right intracardiac shunts increase pulmonary blood flow, which can cause abnormal postnatal remodeling of the pulmonary vasculature. Long-term left to right shunts can gradually produce elevations in PVR, and this elevation can become fixed. In pediatric cardiac surgery patients, pulmonary vascular disease is almost always due to smooth muscle hypertrophy of smaller pulmonary arterioles, and is at least partially reversible with pharmacologic therapy.

CPB in children is also known to attenuate endothelium NO-dependent pulmonary vasodilation,[35] which can be a cause of pulmonary vasoconstriction postoperatively. Children tend to be more vulnerable to pulmonary hypertensive crises occurring in the immediate (1–2 d) postoperative period following CPB. This is particularly true of infants who had preoperative elevations in PVR. In children who have undergone a Glenn or Fontan operation (which leaves them without a subpulmonary ventricle), C.O. will be exquisitely sensitive to elevations in PAP.[36]

Perioperative Use of INO for Pediatric Patients

INO is of potentially greater use in infants and children undergoing cardiac surgery than in adults. Surgery on children with elevated PVR (greater than 7 Woods units) is associated with increased mortality. To determine preoperatively if the elevated PVR is fixed or reversible, children have been evaluated with a variety of nonselective pulmonary vasodilators in the cardiac catheterization laboratory. PVR is measured to determine if there is a decrease with pharmacologic therapy. A case report of an infant with a ventricular septal defect indicated that INO can determine the reversibility of pulmonary hypertension.[37] The elevated PVR (9.1 Woods units) decreased significantly to 3.7 Woods units. The infant required INO in the immediate postoperative period, and was discharged home; however, the PVR returned to baseline after 1 year.

INO, delivered both intraoperatively and postoperatively, appears to be effective in managing pulmonary hypertension in infants and children. Most studies indicate that INO has a significant effect if the PAP is elevated to greater than 50% of systemic pressure. If the PAP is not elevated postoperatively, INO has no effect even if pulmonary hypertension had been present preoperatively.[36,38] In one study the only patients who required INO in the postoperative intensive care unit were those who had pulmonary hypertension and required INO in the operating room following separation from CPB.[38]

Schulze-Neick evaluated the postoperative effects of 50 ppm INO on infants and children who had ventricular septal defect and atrioventricular septal defects.[39] INO resulted in a 43% decrease in PVR and a 28% increase in CI. Right ventricular ejection fraction was significantly improved by 34%. It is clear from that study that INO can cause a clinically significant improvement in RV function and CI in patients with pulmonary hypertension resulting from left to right intracardiac shunts, although possible long-term benefits remain unknown. INO can also be used postoperatively to differentiate elevation in proximal PAP due to abnormal pulmonary vasoconstriction from elevation due to an anatomic obstruction to pulmonary blood flow (eg, a stenotic surgical anastomosis or missed branch pulmonary artery stenosis). If the PAP is unresponsive to INO, an anatomic obstruction to flow should be considered.[40]

In patients undergoing Fontan-type procedures, the PVR can be critical for maintaining C.O. In a study by Gamillscheg, 1.5–10 ppm INO decreased central venous pressure by 15.3 ± 1.4% and transpulmonary artery gradient by 42 ± 8%.[36] Left atrial pressure and mean systemic pressure were increased by 28 ± 8 and 12 ± 4%, respectively, indicating a clinically significant acute hemodynamic improvement.

The effective dose of INO in both infants and children appears to be similar to or slightly higher than that needed for adults. While earlier papers reported using doses in the range of 80 ppm,[41] more recent papers have reported clinical success with doses in the 1–2 ppm range.[36] While INO does lower PVR and can increase RV function and C.O. in postoperative children, research thus far has not demonstrated that use of INO confers a survival advantage beyond that of routine management for pulmonary hypertension (oxygen, sedation, respiratory alkalosis).[38] Nevertheless, there are numerous case reports where INO was deemed critically necessary in weaning from CPB.[42–44] In situations where pulmonary hypertension limits RV function or C.O., INO might be the treatment of choice.

Safety Issues in Pediatric Patients

INO has now been used safely and without complications in the vast majority of cases in infants and children. However, excessive methemoglobinemia secondary to INO is a particular concern in infants. The enzyme that is responsible for converting methemoglobin to hemoglobin is methemoglobin reductase. Methemoglobin reductase activity in neonates is approximately half of that in adults. Elevated methemoglobin levels have been reported in neonates.[45,46]

Practical Operating Room Application

The Ohmeda delivery system (Datex-Ohmeda Division Instrumentarium Corp, Helsinki, Finland) can be set up to deliver INO to the inspiratory limb of the anesthetic circuit. The delivery system is attached to the inspiratory limb near the anesthesia machine to allow for thorough mixing of the NO with the other inspiratory gases prior to measurement of the NO concentration and delivery to the patient. The NO and NO_2 analyzer is attached to the inspiratory limb 6–10 inches from the Y connector to prevent measurement of expiratory NO. Both NO and NO_2 are continuously monitored. We also continuously monitor inspiratory O_2 concentration and recommend immediate measurement of methemoglobin, followed by repeated measurement every 6 hours.

We start nearly all adult and pediatric patients at 20 ppm. If there is no improvement in PAP after 5–10 min the NO is discontinued, though it is important to remember that NO might be effective later. If there is a significant improvement in hemodynamics with 20 ppm INO, we gradually decrease the concentration to approximately 5 ppm unless the response is decreased.

Rebound pulmonary hypertension has been reported upon discontinuation of INO.[47] Although the definition and mechanisms remain unclear, planning for discontinuation of INO is important. Several steps can help prevent rebound pulmonary hypertension: (1) wean from low doses, ie, 1 ppm; (2) compensate for potential increases in PAP by increasing other vasodilators or therapies; and (3) wean after clinical improvement.

Summary

In summary, INO can be of clinical benefit in the setting of RV failure and pulmonary hypertension. Case reports and small studies have demonstrated that INO decreases PVR and can improve RV function and C.O. in patients with cardiac disease. INO has the advantage that it lowers PVR without producing systemic hypotension (which can decrease coronary perfusion pressure and worsen RV ischemia and RV function). In the United Kingdom, a consensus conference group has designated RV failure as one of the clinical indications for the administration of INO.[48] In contrast to RV failure, patients with LV dysfunction can be contraindicated for INO because of the risk of inducing pulmonary edema.

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Discussion

Stewart: What is the experience with INO in patients presenting with right ventricular infarction?

Rich: I can't quote any studies on that in particular. As you know, you are going to have a certain number of patients who come off cardiopulmonary bypass with either biventricular dysfunction, or right ventricular ischemia, or with a right ventricular infarct. It's not nearly as common, obviously, as left ventricular dysfunction, but it does occur. In those patients, we use INO to decrease the afterload on the right ventricle, in the hope of improving right ventricular dysfunction. I can't give you any outcome studies or anything to show that it makes an outcome difference, but I think it has the potential to make a difference.

Stewart: Outside of the post-pump population, are people using NO commonly in the coronary care unit environment, where someone walks in off the street with a right ventricular infarct?

Rich: I don't have any experience with that. Are there other people here that might have had experience with that?

Hess: I guess one of the issues would be, how do you administer it, because many times those patients are not intubated or mechanically ventilated, so it becomes a technical challenge to administer the NO to those patients. Not impossible, but. . .

Channick: In pure right ventricular infarcts, the physiology is one of inability to handle preload, not necessarily an afterload problem where you'd expect NO to work. So in thinking this through, I'm wondering if you'd see efficacy. But I don't know of any experience.

Gerlach: I think these differences between the efficacy on output and pulmonary pressure might be very important also for use in adults: the clinicians really like pulmonary artery pressure (PAP), because they can measure it. They don't like pulmonary vascular resistance, because they say it's just calculated. The physiology is just the other way around. The pulmonary vascular resistance is the regulator and the PAP is a result. The study from Shulze-Neick[1] showed that the nonresponders (due to PAP) were actually responding. They had a tremendous change in cardiac output. And, I was wondering if we might be totally wrong if we define PAP changes as a response. Maybe we would have changes in cardiac output if we used it in acute respiratory distress syndrome. And if we have increased cardiac output with a decreased pulmonary vascular resistance, we don't see any change in PAP.

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Rich: I think that brings up an important point. In this patient population, when you're assessing whether INO is making a difference, it's important to look not just at pulmonary artery pressure; you have a lot of things in your armamentarium, including transesophageal echo, visualizing the heart, cardiac output, and pulmonary vascular resistance. It's important to look at the big picture to see if you're making any difference.

Pearl: Two related questions. In terms of the cardiac surgery type patients in particular, do you view NO as being conceptually different than intravenous vasodilators in terms of its effects on the pulmonary circulation, or is its benefit really just avoiding the systemic effects of intravenous vasodilators?

Rich: I think you're probably right. Clearly, you can get decreases in pulmonary vascular resistance equal to INO with other vasodilators. But, what you really avoid is decreases in systemic vascular resistance.

Pearl: I think I would agree, and that's why many people, for example, pre-heart transplantation, are talking about using NO to assess pulmonary vascular reactivity. If so, in the patient post-cardiopulmonary bypass, who is almost always on multiple vasoactive agents at that time, do you believe that it makes a difference what agents the patient receives in terms of whether you'll see an additional vasodilator effect from NO?

Rich: I think one thing you see commonly post-cardiopulmonary bypass is systemic hypotension, so many times you want to avoid vasodilators. You may not see a lot of additional effects from INO if the patient is already on other vasodilators. But if you're trying to avoid systemic hypotension, you can use INO instead of nonselective vasodilators.

Pearl: We pretty commonly have the setting of left ventricular and right ventricular dysfunction post-bypass, and, thus, are usually trying to reduce the left ventricle afterload, and, thus, are already on some sort of afterload reduction. I can tell you that in the laboratory, whether you're using a nitrovasodilator or another agent does seem to make a difference in terms of the efficacy of NO. But, clinically, we certainly have not been able to prove that.

Rich: There are so many different scenarios for this. I think in the patient you're describing where there's systemic hypertension, certainly you're going to add other vasodilators first. In the presence of other vasodilators, you may not see a lot of vasodilation from INO. But, like I said, I think a significant number of patients are hypotensive, in which case INO is beneficial.

Bigatello: How do you deliver NO in the operating room?

Rich: We've got the folks right over here.

Bigatello: With the INOvent?

Rich: Yes.

Pearl: George, you said that you only use 20 ppm as your maximum dose. We've had post-cardiotomy patients who seem to require 40 or 80 ppm. Have you checked and found that a higher dose doesn't help?

Rich: It is rare that giving more than 20 ppm provides additional vasodilation. It's much more common for us to start at 20 ppm and wean down. I realize there are people here who use higher concentrations than that. I think 20 ppm gives about the maximum effect we see in this patient population. In many cases 20 ppm is probably about 10 times as much as you really need.

Hurford: John, do you want to comment on that, given your experience of using 80 ppm mostly in children with congenital heart disease?

Thompson: We have used 80 ppm since 1990, and have yet to change. I think what we have changed is our weaning response so that within the first hour, more likely than not, we're down to 20 ppm. We do have a handful of patients who do not respond to 20, 40, or 60, and only respond to 80 ppm. There have been varied diagnoses, but we do have those patients.

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Perioperative Use of Inhaled Nitric Oxide for Heart and Lung Transplantation

Emile A Bacha MD

Introduction
Preoperative Use of INO for the Heart or Lung Transplant Candidate
INO as a Bridge to Transplantation in Lung Transplant Recipients
INO for Graft Preservation
Use of INO during Surgery
Postoperative Use of INO
Summary

[Respir Care 1999;44(2):205–209] *Key words: nitric oxide, NO, cardiac transplant, ventricular failure, ventricular assist device, pulmonary.*

Introduction

The perioperative care of heart or lung transplant patients is one of the most formidable challenges clinicians face. As we learn more about the role of endogenous nitric oxide (NO) and the role of vascular endothelial cells in cardiovascular and pulmonary disease, inhaled nitric oxide (INO) therapy has generated a great deal of interest. In healthy humans, NO regulates basal pulmonary vascular resistance (PVR), and helps to maintain a low PVR, compared with the systemic vascular resistance. Pulmonary vascular resistance can be increased by hypoxia, hypercarbia, shear stress, or intrinsic parenchymal pulmonary diseases.[1]

Heart and lung transplantation candidates often have end-stage organ disease associated with hypoxemia and pulmonary hypertension, which complicates their care. The role of endogenous NO in chronic hypoxia remains unclear. The most widely accepted theory at present is that development of chronic hypoxic hypertension is due to endothelial dysfunction.[2] A paucity of NO would impair relaxation and favor excessive pulmonary vasoconstriction in response to various contractile stimuli. This is important in the perioperative period because the severity of pulmonary hypertension increases the risk of complications during heart or lung transplantation. The exact mechanism by which prolonged alveolar hypoxia produces pulmonary hypertension remains unknown.[3]

INO, as a selective pulmonary vasodilator, appears to be an attractive therapy for modulating pulmonary vascular tone for heart and lung transplant patients. Unlike intravenously administered NO donors, INO reduces PVR without producing systemic vasodilation. INO is selective for pulmonary vasodilation because it is rapidly inactivated on binding to hemoglobin.[4] Because INO dilates ventilated regions of the lung, ventilation and perfusion (ventilation-perfusion ratio [V/Q]) matching often improves, and arterial oxygenation increases.[5]

This article addresses the clinical use of INO in patients receiving heart or lung transplants. The preoperative (diagnostic) use of INO for pulmonary vascular reactivity testing, its use as a potential bridge to transplantation, applications in graft protection and preservation, its use during surgery and in the postoperative period, and dosing and timing are discussed.

Preoperative Use of INO for the Heart or Lung Transplant Candidate

Lung transplant candidates are always patients with end-stage pulmonary parenchymal and/or pulmonary vascular disease. Heart transplant candidates often have various degrees of PVR elevation, which has important implications for the postoperative function of the right ventricle. Lung transplant candidates typically have varying degrees of hypoxemia due to poor V/Q matching and pulmonary

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hypertension. In patients undergoing single lung transplantation or sequential bilateral lung transplantation, and in whom cardiopulmonary bypass (CPB) is to be avoided, the non-transplanted lung will have to handle the entire cardiac output through its pulmonary vascular bed. A normal pulmonary vascular bed can tolerate large increases in antegrade pulmonary blood flow as occurs during pulmonary artery clamping for pneumonectomy. But if the vascular bed is not compliant enough, acute right heart failure may result, with the potential need for emergent CPB during pneumonectomy.

The problem is compounded in a heart transplant candidate with elevated PVR secondary to either concurrent lung disease or a longstanding left-to-right shunt that has reversed (Eisenmenger syndrome). Such a patient would ideally be considered for heart-lung transplantation, thereby alleviating both problems and avoiding the risk of right heart failure in the postoperative period. However, because of the current paucity of organ donors, a heart-lung block is most likely to be distributed amongst three recipients, in an effort to help more patients. Therefore, INO might be extremely valuable in patients who otherwise would have to wait for a combined heart-lung transplantation.

Heart and lung transplant candidates undergo extensive testing preoperatively. Heart or lung transplant candidates with pulmonary hypertension and right heart dysfunction may qualify for heart transplantation or single lung transplantation alone if improvement in PVR or ventricular performance can be shown preoperatively (reversible pulmonary vasoconstriction, or non-fixed pulmonary hypertension). For the preoperative evaluation of transplant candidates, INO can be used as an alternative to intravenous pulmonary vasodilators, such as calcium channel blockers, prostaglandins, sodium nitroprusside, or nitroglycerin. In contrast to those drugs, INO does not induce hypoxemia, because the vasodilation it causes occurs only in ventilated areas. Systemic side effects such as hypotension, common with the aforementioned drugs, do not occur with INO.[6] On the other hand, there is recent evidence that INO, administered during preoperative cardiac catheterization, may increase left ventricular filling pressures in patients awaiting heart transplantation.[7] The mechanism is unclear, but could also be related to improvement in right ventricular performance resulting in an increased pulmonary venous return to the left heart.

INO as a Bridge to Transplantation in Lung Transplant Recipients

Conventional medical therapy does not stop the progression of the disease in patients awaiting an organ for transplantation. Chronic hypoxemia, typical in patients awaiting lung transplantation, results in hypoxic pulmonary vasoconstriction, resulting in an even higher PVR. INO reverses the elevated PVR associated with hypoxic pulmonary vasoconstriction.[8] Thus, in patients with reversible vasoconstriction, INO may provide a pharmacologic bridge to lung transplantation. Although more controlled studies are needed, it appears that continuous inhalation of low concentrations of NO is safe.[5,9,10] A few such human cases have been reported, notably in a 40-year-old patient with primary pulmonary hypertension awaiting heart-lung-transplantation.[11] INO also seems to be ideally suited to discriminate between patients needing combined heart-lung transplantation and heart transplantation alone.[12]

INO for Graft Preservation

Lungs and hearts harvested for transplant are considered to be the organs most sensitive to ischemia, compared to other solid organs such as the liver or kidneys. Good preservation of donated organs is essential for successful transplantation. The acceptable ischemic time for a donor human lung or heart is 6 to 8 hours. There is currently no ideal or universally accepted method to preserve hearts or lungs during the period of harvesting, transport, and implantation. The transplanted organ undergoes cold ischemia, followed by warm reperfusion. Clinically, this results in various degrees of ventricular dysfunction, pulmonary hypertension, increased capillary permeability, and increased endothelial adherence and sequestration of neutrophils in the graft.[13] On a cellular level, endothelial dysfunction is the hallmark of ischemia-reperfusion (IR) injury.[14] Selective loss of endothelium-dependent relaxation after flush perfusion with Euro-Collins solution, the most commonly used preservation solution for lung procurements, has been reported.[15] Better preservation of the pulmonary endothelium may reduce postoperative PVR elevation, improve graft function, and exert a preventive effect on IR injury after lung transplantation.

A decreased release of endothelial NO has been observed after reperfusion of transplanted rat lung.[16] Because NO regulates pulmonary vascular tone, aids in maintaining endothelial integrity, and modulates neutrophil adhesiveness and activation, it seems logical to use exogenous NO or NO precursors to protect endothelial function. In a rat model, supplementing the preservation solution with nitroglycerin (an NO donor) resulted in improved oxygenation, improved pulmonary arterial flow, and improved survival after transplantation, compared to preservation with Ringer's solution.[17] The addition of L-arginine, an NO precursor, to the preservation solution also had a beneficial effect on lung function after IR injury.[18] Also, there is evidence that INO attenuates IR injury and improves lung function when administered to the donor during the ischemic period in the setting of non-heart-beating lung transplantation (cadaver ventilation).[19,20] Human organ preservation trials are needed to properly assess the role of exogenous NO and NO donors in organ preservation.

In myocardial IR, NO replacement therapy is being viewed as an attractive way to attenuate neutrophil-mediated injury.[4,21] In several animal models NO pathway supplementation has been shown to enhance cardiac preservation.[22] INO has not been studied in this setting.

Use of INO during Surgery

During lung transplantation, a primary consideration is whether CPB is needed. The need for CPB relates to the ability of the recipient's right ventricle to compensate for the additional elevations in PVR encountered during the transplant procedure. Patients with one or more of the following preoperative findings will likely need CPB during lung transplantation: preoperative room air $P_{aO_2} < 39$ mm Hg, mean pulmonary artery pressure (PAP) > 45 mm Hg, or PVR > 546 $dyn{\cdot}s{\cdot}cm^{-5}$.[23] It is important to monitor PAP throughout the lung transplant procedure because acute pulmonary hypertension can occur during induction and maintenance of anesthesia. Certain drugs such as nitrous oxide, α agonists, and curare can increase PVR. Intraoperative hypoxemia and hypercapnia, particularly during one-lung anesthesia, may also increase PVR and produce right ventricular dysfunction. But, despite optimal management, including the use of INO, some patients still require CPB, which introduces additional risks to the lung graft and the patient. If CPB is necessary, the transplanted lung is reperfused with activated blood elements, which may exacerbate the reperfusion injury. In our experience at the Massachusetts General Hospital, weaning from CPB after lung transplantation has been facilitated by INO administration, presumably because the INO is replacing endogenous NO, which can be deficient because of endothelial dysfunction in the donor lung. Adatia et al[24] found that INO improved graft function in 6 patients post lung transplantation. Following lung transplantation, INO lowered PAP, PVR, and intrapulmonary shunt fraction. A sustained improvement in oxygenation was also noted.

Timing of INO administration has also been a matter of debate. In a pulmonary IR model, INO given immediately at reperfusion was deleterious after 30 min of reperfusion, whereas delaying the administration of NO by as little as 10 min, or treatment with superoxide dismutase (an oxygen free radical scavenger), resulted in improved lung function.[8] This suggests a possible harmful interaction between NO and oxygen free radicals during initial reperfusion. However, most studies have used INO from the onset of reperfusion, with good results.[19,20,25,26]

Postoperative Use of INO

At least 20% of patients exhibit transient graft dysfunction after lung transplantation.[24] The accompanying endothelial dysfunction results in a net decrease in endogenous NO release,[16] which may contribute to pulmonary hypertension. There is a growing body of evidence indicating that INO is beneficial when used postoperatively after experimental and clinical lung transplantation. Most experimental studies used ischemic times of 18 to 24 hours to ensure that a significant IR injury developed. When used during the first 4 hours only after porcine lung allotransplantation, INO was found to have a beneficial effect on graft function, and the effect lasted up to 24 hours after reperfusion (end point of the study).[25] A protective effect was also demonstrated on the contralateral native lung. Pulmonary neutrophil sequestration was significantly reduced, whereas endothelial-dependent relaxation of pulmonary artery rings was not significantly protected after 24 hours. Similar results were obtained in an acute study of allotransplantation in dogs. INO started prior to reperfusion improved graft function during the first 6 hours (end point of the study), and reduced PVR and graft neutrophil sequestration.[27] INO started after reperfusion was not observed to be beneficial in this study. Another recent study reported that INO used 24 hours after porcine lung transplantation resulted in decreased PVR that was proportional to the degree of endothelial damage occurring during IR injury.[28] In a report on the effect of INO on lung transplantation in rats with monocrotaline-induced pulmonary hypertension, INO used for 24 hours after lung transplantation was found to shift pulmonary perfusion toward the native lung, resulting in reduced pulmonary edema of the transplanted lung.[29]

Clinical experience has also been accumulating. Clinical reports are emerging documenting the usefulness of INO in severe reperfusion injury following lung transplantation.[24,30,31] No systemic side effects were noted. The protective effect can only partially be explained by the pulmonary vasodilation afforded by NO. The experimentally-described, decreased neutrophil adherence to endothelium and decreased migration and sequestration into tissues might be in large part responsible for the observed protection.[19,25,32]

Because NO can generate methemoglobin, prolong bleeding time, and inhibit platelet aggregation, the postoperative use of NO should be closely monitored.[5] It seems prudent to limit the concentration and duration of NO therapy following lung transplantation. Recent studies have identified doses of 30 parts per million (ppm) or less to be maximally effective.[19,20,25,26] High doses of NO have the theoretical disadvantage of combining with reactive oxygen species, producing toxic oxygen radicals.[8] We have tried to start INO as early as possible, prior to reperfusion, and kept the concentration as low as possible (usually less than 20 ppm) while still achieving a physiologic response. Weaning INO is performed with a gradual decrease of the INO concentration over several hours following lung transplantation; typically, the INO is off within 72 hours. We have not seen any rebound hypertension following cessation of INO therapy in this patient population. No complications with hemostasis have been observed.

Pulmonary hypertension after heart transplantation is a dreaded complication. It can result in right heart failure, which is very difficult to treat with conventional methods. There are several reports documenting the use of INO for pulmonary hypertension after heart transplantation.[33,34] The reduction in PVR and PAP was comparable with that obtained with intravenous nitroprusside or prostacyclin, but without systemic side effects. After lung transplantation, when the target organ is the same as the organ to which the drug is delivered, INO serves to lower PVR and reduce IR injury through the dual mechanism of local vasodilation and neutrophil sequestration inhibition. Although NO metabolites have been reported to be effective in myocardial IR injury, the short half life of INO (because of its inactivation by hemoglobin) results in no measurable direct effect on the myocardium itself. INO-induced reduction in PVR indirectly reduces right ventricular afterload.

INO may be also beneficial following CPB. Prolonged CPB results in pulmonary vascular endothelial cell dysfunction and increased pulmonary vascular tone.[35] Several recent reports studied the intraoperative effects of INO during cardiac surgery. Patients treated with NO showed decreased PVR following CPB.[35,36,37]

Summary

INO is emerging as a useful diagnostic tool in patients awaiting heart or lung transplant, allowing us to distinguish between those patients with reactive pulmonary vasculature and reversible pulmonary hypertension, and those with fixed pulmonary hypertension. The postoperative use of INO after heart or lung transplantation is bolstered by a large experimental body of work as well as recent clinical evidence, and is becoming an essential part of the clinician's armamentarium in caring for these often critically ill patients. Further studies are needed to define the exact timing, dose, and mechanism of action of INO in the transplant population.

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Discussion

Dr Bacha was unable to attend the Journal conference, and presented his paper to his colleagues, Dean R Hess PhD RRT and William Hurford MD, at Massachusetts General Hospital. The discussion generated by his presentation follows.

Hurford: Regarding the timing, has there been work done using NO or administering NO to the donor before transplantation?

Bacha: Clinically, no. I mean, I don't think there have been any studies in humans, although I don't see what the down side would be. So it has not been done, but in animals it has been done. In experimental lung transplantation INO has been used at different time intervals. There was a debate as to whether using INO or other NO donors was actually detrimental if you gave it too early on, because it would react with toxic oxygen radicals.

Hess: Producing peroxynitrite radicals?

Bacha: Exactly. We did not measure the oxygen radicals, but we did not find any detrimental effects from using INO right at the beginning of reperfusion. It may be a question of the dose, too, because giving 80 ppm, for example, might provide enough NO to combine with oxygen radicals, whereas giving 30 ppm might just be enough to be beneficial.

Hurford: Do you think there is a key phase in the ischemia reperfusion process that determines whether NO is going to be beneficial or detrimental?

Bacha: Well, I think the most important lesions in ischemia-reperfusion injury happen in the first 15 to 30 minutes. That's why I think it's really important to administer NO at that time. I think the most common mistake is to start INO too late, and then the damage is done, and then people say it's not working well. It may not be potent enough to reverse the effects of ischemia reperfusion injury, but it certainly blocks the response. Just doing those pig experiments was really interesting. You could tell (it was a blinded study) which pigs were receiving INO because they would be doing better clinically than the other pigs. Those pigs were on INO as donors, from the beginning of the experiment.

Hess: Have you,or anyone, looked at bronchoalveolar lavage or cytokines?

Bacha: Yes, it's been done. There's a group[1] that looked at that, but we did not. We were looking for other signs—for example, activation of neutrophils and sequestration of neutrophils. This group did find that with INO there were less neutrophils in bronchoalveolar lavage than without INO. Those neutrophils, interestingly, were less activated when INO was administered. So the current evidence points to an effect of INO on circulating neutrophils, as well as on the endothelium, which is something that hasn't been worked out really well yet. But this group did find that the activation of the neutrophils in bronchoalveolar lavage is less with INO. We found that adherence of circulating neutrophils to pulmonary artery endothelial cell cultures is less with INO, which means that somehow the INO has to have an effect on those circulating blood cells, and not only on the endothelium, which is the other commonly accepted idea.

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Hurford: If you were to design a clinical study to decide whether you should use INO, what would be your end points, and how would you do it?

Bacha: That's a tough question. If it's a study, then you would have to blind it and give half your recipients a placebo, and the other half INO. But I would do it systematically on everybody, not wait for evidence of damage (ischemia reperfusion injury), and then, obviously, measure blood gases, cardiac outputs, all the clinical parameters that you can. Bronchoalveolar lavage would also be interesting. So, measure PVR at specific time points, and survival, look at x-rays, grade the x-rays.

Hurford: Certainly get through that initial episode. The early survival is relatively high, but, the ischemia reperfusion episode is clinically unpleasant because of the use of extracorporeal membrane oxygenation (ECMO) and increased intensity of mechanical ventilation, and duration of mechanical ventilation.

Bacha: Right. I agree, and because we have so much technical support (you mentioned ECMO) they do get through, but it's after 2 or 3 months in the intensive care unit, and they are debilitated and so forth. I'm not saying INO is a magic bullet, but it's certainly helpful, and the other impression that people who do a lot of lung transplantations get is that if a patient has had such a stormy course or has had ischemia reperfusion injury, it's sometimes difficult to differentiate between ischemia reperfusion and, for example, acute rejection. From a long-term perspective, those patients do worse than patients who just fly through the operation. I think it's a logical deduction, but it's also a clinical observation. Would you agree?

Hurford: Yes. I don't know of anybody who's looked at late effects after lung transplantation.

Bacha: I don't think anybody has.

Hess: Is there any basis for a late benefit?

Bacha: In theory, I would think that avoiding damage to the lung, just avoiding the activated neutrophils getting into the tissues and releasing their cytokines and so forth, would be beneficial in terms of preserving parenchyma of the lung and lung function, long-term. But, again, I don't think anybody has studied or proven this. In terms of heart transplantation, it's a bit different, because it's more of a tool that we can use in case of pulmonary hypertension. It's not effective against myocardial ischemia-reperfusion injury, per se. If you get the myocardial ischemia reperfusion phenomenon, INO is obviously not going to help, because it binds with hemoglobin, and it's not going to get to the myocardium. It's certainly very helpful in right heart failure. Right heart failure after transplantation is something that's very difficult to deal with, and there aren't any good drugs for that.

Dr Bacha's presentation to his colleagues at Massachusetts General Hospital was videotaped and shown to the participants in the Journal conference; their comments follow.

Hess: We do have a few minutes if any of you would like to add your comments to Dr Bacha's presentation. I know Al Head has done some work with NO and transplantation, and Bill (Hurford) has thought about some of these issues, and perhaps some of the others of you as well. Unfortunately, Dr Bacha is not here to take questions.

Gerlach: I think you described at the end that circulating neutrophils are not activated by INO: the question again comes up if NO is working systemically or not. A very interesting model would be to inflate just one lung during transplantation, because this would prove if this is a local action. The other question, of course, is if it's working systemically, and this was shown by these in vitro experiments. Therefore, it should be discussed if local admission of NO gas or NO-donating drugs might be beneficial. I don't know if there are any data.

Hurford: In one of Emile's papers[1] he was able to show a reduction in myeloperoxidase activity in the lung that was not transplanted, so the native lung appeared to have a reduction in neutrophil accumulation, which would suggest that it's a systemic effect. Now, is it a systemic effect of neutrophils just passing through the lung and being activated, because all the neutrophils will get there anyway, eventually, or is it due to this pool of nitrosylated proteins and hemoglobins? I don't think there's any way of teasing that out. But it does seem to be a systemic effect, not just to the one transplanted lung.

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Head: I think it certainly points toward a systemic effect with INO for the reasons that you mentioned. I think that study would be very good. Certainly NO donors would not be good in this patient population for oxygenation reasons, because of shunting and for all the reasons we give INO to begin with. But it's a very difficult study to do. In our studies, intraoperatively, it's a very dynamic situation. Often these patients are not stable enough to obtain clean data, and it's really quite a struggle to get controlled studies. I was trying to look at NO effects in both the diseased lung and the donor lung. We still haven't completed our data collection, but we want to see if we can turn on endothelial NOS (eNOS). We get tissue protein from the diseased lung and also get tissue from the implanted lung, and that's in process now. I can't tell you what the answer is yet: I want to know myself. However, we should be able to see if we can turn eNOS on and see if it's regulated as far as the endothelial portion. But, again, this is an extremely difficult study to do in these transplant patients. We have seen improvement in oxygenation. The typical things that you can see with NO, but that's really a vasodilator effect for the most part.

X-rays, I think, are very difficult to interpret postoperatively in these patients, and Emile (Bacha) mentioned grading x-rays as an end point. However, in looking at the x-rays postop in our patients, I think that it's very difficult to make any type of good assessment regarding NO effects.

Gerlach: I would be cautious to interpret this as if NO does not work during ischemia. During ischemia the tissue produces tons of nitric oxide; this was shown by Zweier with electron paramagnetic resonance technology.[1] An ischemic organ produces much more nitric oxide directly from nitrite than via the NOS pathway. It was shown in lung transplant recipients, that directly after reperfusion and reinhalation, you have lots of NO in the exhaled gas. I will show this tomorrow. But this is probably produced in the nonperfused lung. So the only conclusion is that it's not useful to use INO in ischemic lungs, because the lung has enough.

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Head: I agree with your points. Also, I think the best time to use NO may be during harvesting. Because what you want to do is protect the endothelium at that time. It's the dysfunctional endothelium, because of ischemia and then reperfusion that is probably starting the cascade of problems. So, there are studies[1,2] in which they looked at using NO donors in preservation solution, and they seem to have the best outcome. Those studies were all animal studies in dogs and rats. I haven't seen any human studies using NO donors and preservation solution, but that's probably the best approach, and you may or may not need INO intraoperatively for other reasons. However, it's during harvesting and the ischemia reperfusion period that NO is probably most needed.

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Long-Term Use of Inhaled Nitric Oxide for Pulmonary Hypertension

Richard N Channick MD and Gordon L Yung MD

Introduction
Pathophysiology
Pathogenesis of Pulmonary Hypertension; Role of Nitric Oxide
  Inhibition of Platelet Aggregation
  Inhibition of Vascular Smooth Muscle Cell Proliferation
Practical Delivery System for Ambulatory INO Delivery
Clinical Applications
  Acute Vasodilator Testing
  Long-Term Uses of INO
  Primary Pulmonary Hypertension
  INO and Idiopathic Pulmonary Fibrosis
  Chronic Obstructive Pulmonary Disease
  Congenital Heart Disease
Summary

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Introduction

Chronic pulmonary hypertension is a life-threatening physiologic consequence of a diverse group of disease processes, some common (for example, chronic obstructive pulmonary disease [COPD]), and some rare (such as primary pulmonary hypertension). Pulmonary hypertension can be due to diseases that affect the pulmonary vasculature primarily (for example, primary pulmonary hypertension) or secondarily (such as parenchymal lung disease and cardiac disease). A useful diagnostic classification is shown in Table 1. To consider the potential applications of the pulmonary-selective vasodilator inhaled nitric oxide (INO) in these diseases, it is important to first review the pathogenesis and pathophysiology of pulmonary hypertension and to outline the role of nitric oxide in these processes.

Pathophysiology

Pulmonary hypertension develops when the cross-sectional area of the pulmonary vascular bed is reduced. Many processes can lead to this compromise of the vasculature, including vasoconstriction, vessel obstruction, and vascular obliteration. Pathophysiologically, chronic elevation in pulmonary arterial pressure causes right ventricular hypertrophy and enlargement. The ability of the right ventricle to compensate for increased afterload likely determines the natural history and clinical course of a patient with pulmonary hypertension, and if right ventricular performance can be improved, symptoms and survival also improve.

Disorders leading to pulmonary hypertension include processes affecting the pulmonary vasculature as a primary phenomenon and illnesses in which pulmonary hypertension results from insults occurring outside the vasculature (secondary causes). Secondary causes include pulmonary parenchymal disease (restrictive and obstructive lung disease), cardiac disease (septal defects, valvular disorders, cardiomyopathy), and disorders of ventilation. Primary vascular disorders include chronic unresolved pulmonary emboli in large vessels and primary pulmonary hypertension involving small vessels diffusely (See Table 1).

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Table 1. Diagnostic Classification of Disorders Leading to Pulmonary Hypertension

- Non Pulmonary Vascular
  - Lung Disease
    - Restrictive: Pulmonary fibrosis
    - Obstructive: COPD, CF
  - Heart Disease
    - Congenital Heart Disease: ASD, VSD, Anomalous vein
    - Valvular Heart Disease: Mitral stenosis
    - Left Ventricular Disease: Cardiomyopathy
  - Disorders of Ventilation
    - Obesity—hypoventilation syndrome
    - Sleep apnea
- Pulmonary Vascular
  - Large vessel
    - Chronic thromboemboli
    - Mediastinal fibrosis
    - Tumors
  - Small vessel
    - Primary pulmonary hypertension
    - Vasculitis

COPD = chronic obstructive pulmonary disease; CF = cystic fibrosis; ASD = atrial septal defect; VSD = ventricular septal defect.

In addition to pulmonary arterial hypertension, gas exchange derangements can also be present in several of these conditions. In pulmonary parenchymal disease-induced pulmonary hypertension, intraparenchymal shunting and low ventilation-perfusion ratio (V/Q) areas are often present. Septal defects and severe primary pulmonary vascular disorders can also be associated with hypoxemia, through intracardiac right to left shunting and/or low mixed venous arterial oxygen tension (P_{aO_2}) secondary to low cardiac output.

From a clinical standpoint, pulmonary hypertension may be "fixed" (indicating predominantly obstruction or obliteration), or "reversible" (indicating vasoconstriction). In general, the greater the vasoconstriction the more clinical success will be obtained with a vasodilator. This fact has been well demonstrated in primary pulmonary hypertension (PPH).[1] To determine a patient's degree of vasoreactivity, it is necessary to administer a vasodilator while measuring pulmonary hemodynamics. In PPH, only 25% of patients have significant reactivity,[2] and this percentage is probably even less in secondary forms of pulmonary hypertension.[3]

Patients with significant parenchymal lung disease face an additional pathophysiologic challenge. In these patients, a "nonselective" vasodilator may actually worsen hypoxemia by vasodilating poorly-ventilated and nonventilated lung regions.[4] In contrast, a "selective" vasodilator (one that is preferentially delivered to and acts on better-ventilated lung regions) may improve oxygenation. INO appears to be such an agent.

Pathogenesis of Pulmonary Hypertension; Role of Nitric Oxide

The mechanisms involved in the development and maintenance of pulmonary hypertension are complex and variable, depending on the cause. The crucial role of the vascular endothelium is clear. Many mediators, including nitric oxide (NO), are now known to be released by the endothelium. These substances may be protective, by maintaining the vasculature in a relaxed, nonproliferative state (for example, NO or prostacyclin), or detrimental if they favor vasoconstriction and vascular cell proliferation (for example, thromboxane A2 or endothelin 1). An imbalance of actions of these mediators is thought to be responsible for many of the pathophysiologic changes in pulmonary hypertension.[5]

In healthy humans, basal production of endothelium-derived NO, by way of the enzyme NO synthase (NOS), may help to maintain and modulate pulmonary vascular tone.[6,7] However, the precise role of NO in pulmonary hypertension is not well known.

In conditions such as sleep apnea and COPD, hypoxia is likely to contribute to the development of pulmonary hypertension through development of medial hypertrophy, neomuscularization, and vasoconstriction. However, the effects of both acute and chronic hypoxia on NO production and activity is debated. There are conflicting reports as to whether hypoxia leads to reduction[8–11,12] or augmentation[13–15] of NO production or endothelial NOS (eNOS) expression. Even less is known about the pathogenetic role of NO in human pulmonary hypertension. A fundamental obstacle lies in the fact that patients typically present with advanced pulmonary vascular remodeling. Therefore, one cannot replay the processes that led to the advanced disease state.

Dinh-Xuan et al discovered that various disease states (including Eisenmenger syndrome, COPD, and cystic fibrosis) are associated with a decrease in endothelium-dependent relaxation.[16–19] Using immunohistochemical techniques, Giaid and Saleh found decreased endothelial NOS in patients with primary pulmonary hypertension.[20] Their findings suggest that pulmonary hypertension is at least associated with impaired NO production.

In addition to its selective pulmonary vasodilating effects, INO has been identified as having 2 other potentially beneficial effects: inhibition of platelet aggregation and inhibition of cell proliferation, both of which may be important in the context of chronic pulmonary hypertension.

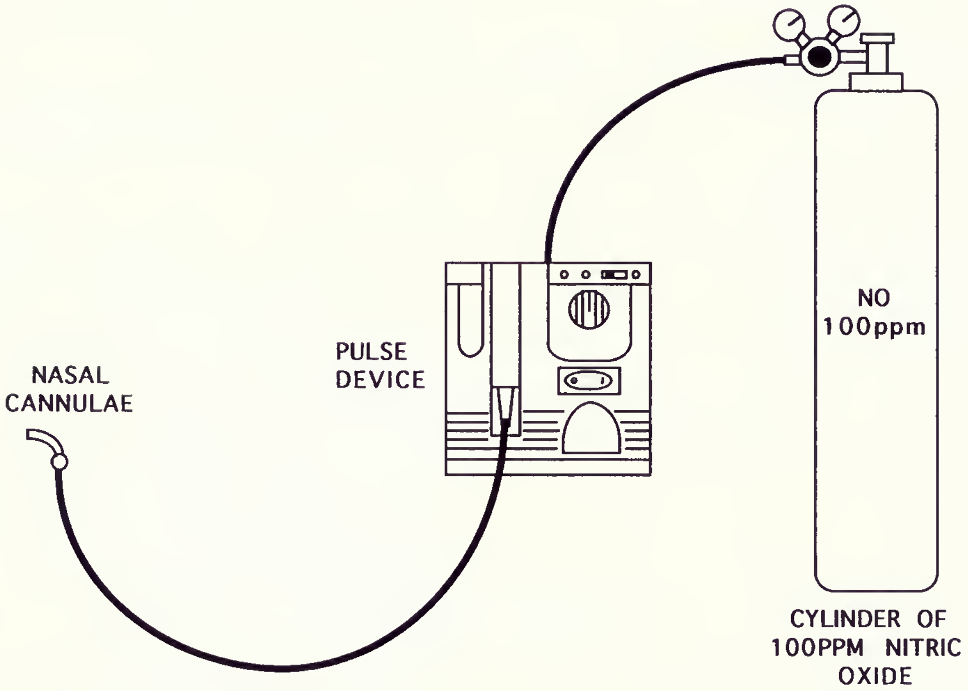

Fig. 1. Schematic representation of system for pulsed delivery of inhaled nitric oxide to ambulatory outpatients.

Inhibition of Platelet Aggregation

There is evidence that abnormal platelet activity and other coagulation abnormalities occur in PPH patients.[21,22] INO has been shown to inhibit platelet aggregation and platelet-mediated pulmonary thrombosis in rats.[23] The clinical role of INO in preventing thrombosis in pulmonary hypertension, however, is not known.

Inhibition of Vascular Smooth Muscle Cell Proliferation

Pulmonary hypertension-associated vasculopathy is characterized by proliferative changes, such as intimal thickening, medial hypertrophy, and plexiform lesions. Experimental evidence suggests that INO has anti-proliferative properties that can potentially alter the vascular changes seen in pulmonary hypertension. NO-producing vasodilators, such as glyceryl trinitrate, have been found to inhibit proliferation, migration, and deoxyribonucleic acid synthesis of smooth muscle cells and fibroblasts,[24,25] as well as to inhibit neointimal proliferation after vascular injury.[26]

Practical Delivery System for Ambulatory INO Delivery

The INO delivery systems used in intubated, mechanically ventilated patients cannot be used in the home setting, so delivering INO to outpatients required development and testing of a safe, practical system. An ideal home delivery system would: (1) require no dilution to the source tank, (2) maximize efficiency of gas use, and (3) pose minimal environmental risk. Pulsed or bolus delivery of INO via nasal cannula seems to fulfill these criteria.

At University of California San Diego Medical Center, our delivery system consists of a source tank of 80–100 parts per million (ppm) INO connected to a demand-activated pulsing device (Figs. 1 & 2), which is connected to the patient by a nasal cannula (up to 30 feet in length). The patient triggers INO delivery each time he or she generates a negative pressure of 0.5 cm H_2O during inspiration. Approximately 18 mL of the gas carrying the INO is pulsed into each inspiration. Although the duration of each pulse can be varied, the flow is kept constant at 10 L/min. The gas is delivered at the beginning of each inspiration to maximize the amount of INO reaching the alveoli. Patients who require supplemental oxygen use a split nasal cannula that separately delivers INO and oxygen, to minimize mixing.

The concentration of INO that reaches the alveoli will depend on the tidal volume (V_T) and inspiratory flow of each breath. However, we have found that patients who demonstrate acute pulmonary vasoreactivity to 10–20 ppm INO via face mask respond similarly with the pulsing system described above.

By limiting INO delivery to the initial inhalation phase, this system maximizes the concentration of INO delivered to the alveoli while using the minimum amount of INO,

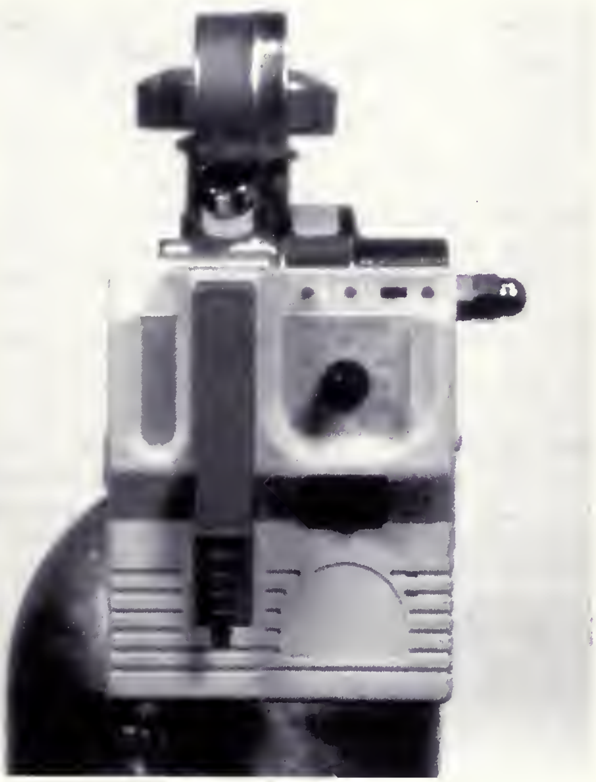

Fig. 2. Pulsed delivery system currently used at University of California San Diego Medical Center for outpatient administration of inhaled nitric oxide.

thus maximizing the longevity of the INO source tank. Since most of the INO reaches the alveoli, where it is then absorbed, minimal INO is exhaled into the ambient air.

We use 2 sizes of INO source tanks. Large tanks (no. 88 cylinders) have a 2,200 L capacity and are put in different rooms of the patient's home in order to allow continuous use. Patients are also supplied with smaller tanks (D size cylinders, 300 L capacity) that allow short trips outside the home. Depending on the patient's level of activity, each large tank lasts 2–3 days and small tanks last for 8–16 hours. A source tank of higher NO concentration would last longer but would also pose a greater environmental hazard.

Clinical Applications

In pulmonary hypertension, data regarding the efficacy of both short-term and long-term INO treatment consist mainly of case reports and small case series. There has not yet been a randomized controlled trial of INO in chronic pulmonary hypertension.

Acute Vasodilator Testing

Determining the degree of acute vasoreactivity in patients with pulmonary hypertension is vital to deciding on appropriate therapy. Because of the ease of delivery using systems like that described above and the apparent absence of adverse effects, INO is potentially an excellent vasoreactivity testing agent. INO's acute pulmonary vasodilator response rate and magnitude are similar to other vasodilators, including prostacyclin[27] and calcium channel blocking agents. At University of California San Diego Medical Center, an INO vasodilation response study can be completed in 15 min in the catheterization laboratory or intensive care unit.

Table 2. Potential Applications of Long-Term Inhaled Nitric Oxide

Primary pulmonary hypertension
Congenital heart disease
Fibrotic lung disease
Obstructive lung disease

Long-Term Uses of INO

In addition to smooth muscle cell relaxation, INO has anti-inflammatory effects, inhibits smooth muscle cell proliferation, decreases platelet aggregation, and has anti-bacterial and tumoricidal properties. Thus, exposing the airway epithelium, alveoli, and pulmonary arteries to long-term INO might have a variety of beneficial effects. Potential long-term applications of INO are summarized in Table 2.

Primary Pulmonary Hypertension

Patients with PPH typically develop a severe small-vessel vasculopathy, often leading to pulmonary arterial pressures as high or higher than systemic pressure. Progressive right ventricular enlargement and failure commonly occur. Median survival from the time of diagnosis is approximately 3 years. The severity of right ventricular dysfunction, as assessed by right atrial pressure, is the strongest (negative) predictor of survival. Likewise, an acute vasodilator response (defined as reduction in PAP and pulmonary vascular resistance (PVR) by at least 20%) infers a very favorable prognosis with vasodilator treatment, typically oral calcium channel blockers.[1] Unfortunately, only 20–25% of patients fall into this acute vasoreactive category. In addition, calcium channel blockers have several potentially hazardous side effects, including arrhythmia, negative inotropy, peripheral edema, and gastrointestinal side effects. In many patients, these adverse effects necessitate discontinuation of the agents.

Another agent, prostacyclin, was recently approved by the U.S. Food and Drug Administration for use in PPH. Prostacyclin must be delivered intravenously because of its instability and pH requirements. Continuous intrave-

Table 3. Hemodynamics at Baseline and After 12 Weeks of Inhaled Nitric Oxide in 5 Primary Pulmonary Hypertension Patients

Pt.	Mean RA (mm Hg)		Mean PAP (mm Hg)		C.O. (L/min)		PVR (dyn·s·cm^{-5})		a-vO_2 difference (mL/dL)	
	BL	12 wks	BL	12 wks	BL	12 wks	BL	12 wks	BL	12 wks
1	17	11*	51	50	3.2	4.3*	1062	729*	7.6	6*
2	24	11*	47	38*	2.7	3.3	1113	851*	9.4	7.6*
3	10	15**	74	77	3.1	3.5	1589	1455	ND	ND
4	19	12	44	37	3.4	2.7**	710	970**	6.7	7
5	20	26	58	49	2.7	1.6**	1181	2064**	ND	ND

RA = right atrial pressure; PAP = pulmonary arterial pressure; C.O. = cardiac output; PVR = pulmonary vascular resistance; a-vO_2 = arteriovenous oxygen content difference; BL = baseline; * at least 20% improvement; ** at least 20% worsening; ND = not determined.

nous prostacyclin has been shown to improve exercise tolerance and survival in PPH patients. Interestingly, some patients who achieve substantial reductions in pulmonary arterial pressures on long-term prostacyclin have no acute vasoresponsiveness to this agent. This apparent paradox has raised the possibility that prostacyclin may be working through mechanisms other than pulmonary vasodilation, namely platelet inhibition or cell growth inhibition. In other words, there is the possibility of remodeling or healing the diseased pulmonary vascular bed.

Like oral vasodilators, intravenous prostacyclin has potential adverse side effects, including systemic vasodilation, which may actually worsen gas exchange in some patients. In addition, intravenous prostacyclin requires mixing daily and maintaining an indwelling catheter.

Preliminary reports indicate that long-term INO treatment is a practical therapy for PPH patients, both in and out of the hospital.[28,29] Snell et al reported a PPH patient who received INO treatment for 68 days while hospitalized, awaiting a transplant.[28] Using our ambulatory delivery system, we have reported INO treatment for up to 1 year.[29]

At University of California San Diego Medical Center, several patients have now received INO treatment for up to 3 years, and the pulsed INO delivery system has functioned well. Baseline and 12-week hemodynamic data for 5 patients are shown in Table 3. In 2 of those 5 patients, significant hemodynamic improvement was observed, although the effects were variable. Of interest, 1 patient who was continued on INO demonstrated gradual improvement in pulmonary hypertension and right ventricular function during the first year of INO treatment. In fact, pulmonary arterial pressures in this patient normalized. This response suggests that INO, similar to prostacyclin, may induce a beneficial remodeling of the pulmonary vasculature, possibly through similar biologic effects (inhibition of platelet aggregation and cell growth). There have been no adverse effects reported by any patient in this study. No obvious pulmonary toxicity has occurred in patients treated with long-term low-dose INO. Generation of NO_2 or methemoglobin does not appear to be a concern in this group. Confirming the efficacy of long-term INO in PPH and elucidating its mechanisms of effect will require a large randomized trial.

INO and Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a disease of unknown etiology, characterized by progressive thickening of the alveolar interstitium and secondary pulmonary vascular destruction. As the disease progresses, patients often develop severe hypoxemia and secondary pulmonary hypertension, largely as a result of shunt and ventilation-perfusion inequalities.[30,31] Severe O_2 desaturation during exercise is common and generally of much greater severity than that seen in COPD.

In several reports, INO has been shown to improve oxygenation and reduce the degree of pulmonary hypertension in patients with primary and secondary forms of pulmonary fibrosis.[32–34] The effects of INO are likely to be a combination of reducing pulmonary vascular resistance (by vasodilation) and reducing shunt fraction, as is observed in acute lung injury (acute respiratory distress syndrome (ARDS]).

Since hypoxemia and pulmonary hypertension contribute significantly to the morbidity and mortality of patients with IPF, long-term INO may be useful in treating this form of parenchymal lung disease. But, again, confirmation of this hypothesis awaits large clinical trials.

Chronic Obstructive Pulmonary Disease

Existing reports on the efficacy of INO in COPD are conflicting. Adnot et al studied 13 patients with COPD and pulmonary hypertension, and found that 40 ppm INO led to a small reduction in pulmonary artery pressure and improvement in P_{aO_2}.[35] Similarly, Yoshida et al found that a combination of INO and O_2 increased P_{aO_2} more than did O_2 alone.[36]

In contrast, Barbera et al found that INO induced a small decrease in P_{aO_2} by worsening V/Q heterogeneity.[37] And another study of 14 patients with COPD found that INO increased ventilation to poorly-perfused or unperfused lung regions, although no change in P_{aO_2} was noted. Hopkins and co-workers confirmed in an animal model of variable balloon airway occlusion that when complete occlusion was induced (shunt), INO did reduce shunt fraction.[38] On the other hand, when partial occlusion was present, causing V/Q heterogeneity and not shunt, the response was variable, with V/Q heterogeneity improving in some subjects and worsening in others.

Another study found that, in COPD patients, INO decreased P_{aO_2} while they were at rest, but prevented a decrease in P_{aO_2} during exercise.[39] This suggests that, with exercise, INO is preferentially distributed to well-ventilated lung units.

These studies, taken together, confirm the heterogeneity of gas exchange abnormalities in COPD patients. Although abnormalities in NO production have been observed in lungs from patients with severe COPD, the contribution of these abnormalities to the physiologic derangement is unclear. From a clinical standpoint, it is not clear whether long-term INO will have an overall beneficial effect in this group. Supplemental long-term oxygen, on the other hand, has been clearly shown to improve survival. Although INO may have a greater pulmonary vasodilator effect, patients with COPD generally do not have severe pulmonary hypertension, in contrast to patients with fibrotic lung disease. Although the beneficial effect on exercise P_{aO_2} is intriguing, translating these findings to clinical efficacy will require large randomized studies in a varied COPD population.

Congenital Heart Disease

Elevated PVR is a common finding in patients with congenital heart diseases, such as atrial and ventricular septal defects and anomalous pulmonary venous drainage. The cause of the elevated PVR can be complex, and involves, to varying degrees, reversible factors, such as hypoxic vasoconstriction and vascular medial hypertrophy, and irreversible vascular changes, such as intimal proliferation and plexogenic vascular lesions. It is important to note that the microvascular changes seen in these diseases are not different from those observed in PPH patients, suggesting similar pathogenetic mechanisms.

Surgical correction of an intracardiac shunt in the presence of fixed and elevated PVR may precipitate acute right ventricular failure, low cardiac output state, and even death. Assessing the reversibility of elevated PVR is therefore an important part of the preoperative evaluation in many of these patients.

Because of its pulmonary vasoselectivity, INO is a useful tool in assessing the vasodilator capacity of the pulmonary vascular bed.[40–43] Patients who, despite an elevated PVR, demonstrate a significant pulmonary vasodilator response might still be considered candidates for corrective cardiac surgery.[43] In these patients, use of INO may potentially eliminate the need for lung biopsy for morphologic determination of vascular changes.

Many studies have demonstrated the role of INO after corrective surgery for a variety of congenital heart diseases.[44–46] INO appears to ameliorate postoperative pulmonary hypertensive crises and correct post-cardiopulmonary bypass endothelial dysfunction.[47] In addition, improvement in right ventricular function and cardiac output in these patients has also been demonstrated.[48] There are no data, however, regarding the efficacy of long-term INO in ambulatory patients with congenital heart disease.

Whether long-term ambulatory INO will be clinically useful in patients with congenital heart disease is currently unknown. However, from a practical standpoint, application of the ambulatory delivery system to both pediatric and adult patients with congenital heart disease is feasible.

Summary

Unlike the large amount of data, including data from randomized trials, that have examined the efficacy and safety of INO in acute respiratory failure and PPHN, data regarding delivery of INO in chronic cardiopulmonary disease are relatively scant. Preliminary published and unpublished data suggest that delivery of INO for up to 3 years is feasible for outpatients with pulmonary hypertension. In individual cases there appears to be efficacy. Finally, no obvious adverse effects have been identified, despite long-term continuous INO.

Many questions remain. Which pulmonary hypertensive disorders will benefit? What is the true efficacy of long-term INO? Are there any currently-unrecognized long-term toxicities from INO therapy? These questions await large-scale randomized trials. However, the potential for INO "making it" to the home appears to be great.

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Discussion

Stewart: Is it generally well-accepted that if a patient responds to INO they are candidates for long-term oral agents?

Channick: Yes. There are good data on that. Acute response to NO correlates with both the acute response to prostacyclin and the response to calcium channel blockers. Obviously, NO is advantageous over a calcium channel blocker trial because it's safer.

Stewart: So they should be comfortable with me just giving a trial of INO rather than attempting oral agents?

Channick: Yes. In fact we do them in the cardiac catheterization lab or in the unit, and with that system we literally wheel it up and in 10 minutes we have the answer.

Stewart: What does it cost the patient to go home on long-term INO?

Channick: Right now it costs nothing.

Stewart: But what type of cost are we talking about?

Channick: It's obviously being studied on a research protocol, so the cost is really the usual cost of studies: the lab studies we get, the cost of the gas, the tanks. Ohmeda, now INO Therapeutics, has been extremely generous through their donation program in supplying the gas for these patients, which is no small feat. But we're talking about up to 40 portable tanks arriving and patients taking a truckfull home with them. But keeping it supplied has been very difficult. In all honesty, the limiting factor in this study in terms of enrolling or doing a larger study has been the tank situation. I can tell you that this project gets funded in the same way that many studies get funded: a little here, a little there, and take out your VISA card at times.

Pearl: Just to follow up on that comment about NO and calcium channel blocker response, my understanding of the literature is that failure to respond to NO will conclusively rule out response to calcium channel blockers, but around 20% of patients who are NO responsive are not calcium channel blocker responsive, so you may still have to test the responders.

Channick: That's a very valid point. How you define a response is interesting to me. In the pulmonary hypertension world we've always used the 20% rule: you need to drop the pulmonary artery pressure and pulmonary vascular resistance by 20% or more. That came from a study using calcium channel blockers that showed that you get a spontaneous variability of up to 20% if you leave a Swan in for 24 hours. Therefore, you need to see a greater than 20% response to show that the patient is "responding." But with NO that's not at all the case, because the effect of NO is so fast that we can all see that they're responding. You turn it on, the pulmonary artery pressure goes down; you turn it off, it goes up. Maybe less than 20%, but it's still a response. So, really, it depends on how you define a response. The question is really going to be outcome. In the patients who respond to NO and are placed on calcium channel blockers, do they have favorable outcomes, similar to what the acute calcium blocker data showed? Those studies clearly haven't been done, but our general approach is that if patients have a significant acute NO response, they clearly deserve a long-term trial of calcium channel blockers before we say they're going to fail. So it's complicated.

Stewart: How do you choose the proper dose of calcium channel blockers based on response to NO? We were selecting our dose of calcium channel blocker based on how much they needed to respond over a 24-hour period.

Channick: We do it one of two ways. In some patients who are quite ill, we will keep them in the hospital and load them up with calcium channel blockers until we see a response. We're really doing this to make sure they don't decompensate while you're loading them up. In patients who are less sick, for example a pulmonary artery pressure of 40 or 50 in a Class 2 patient, you could start calcium channel blockers as an outpatient. We're actually using amlodipine now as our first-line calcium channel blocker. I'm pretty convinced that it's a safer drug for having fewer negative cardiac effects. So we'll usually start them at 5 mg and increase the dose as an outpatient, then follow them clinically and by echo.

Head: I find this work to be very interesting. I really think this is a good move and a different direction for NO outside the ICU setting. I've been approached by a pulmonologist in our transplant section to also try to set up an NO nasal delivery system much like what you've done. This is an excellent method for delivering INO, but it concerns me about patients who may have rebound at home under certain circumstances, if they take their nasal prongs off for any significant time period. I've had a difficult time accepting that role of responsibility. I was wondering how you handle this matter and has that occurred with any of your patients on NO prongs? How have you handled this situation in your protocol?

Channick: That's a very fair question, one that I'm asked repeatedly. We've looked at 8 patients. Only one patient had a clinically important rebound. The patient, when she took off her NO, would start to feel lightheaded within 20 seconds, and then she'd put it back on. She didn't suffer any ill events at home. The other patients have not reported similar episodes. The data, therefore, don't suggest a dramatic rebound. I can't explain why that is. Clearly, when you look at the ARDS group, the experience is different. Whether that relates to the fact that we're delivering just a small bolus, or the way it's being delivered, I don't know. Maybe the endogenous production of NO is different in patients with severe chronic lung disease and pulmonary hypertension than in an acutely inflamed ARDS patient; it's a different disease process.

Thompson: We're starting to use your system in pediatrics, and I'm constantly asked how many parts per million are we delivering. And, as many times as I talk around it, can you give me any advice?

Channick: I was hoping no one would ask. But there is obviously an issue of dose. My first answer is "Does it matter?" I don't mean that facetiously, but when we're talking about chronic long-term use, you're talking about NO exposure over months or years. Does the actual concentration matter, or is it the cumulative dose over time that matters? Clearly in patients in whom you see an acute response, you can do a dose-response study. Most patients don't have such a response, so we really have used a somewhat arbitrary dose. To answer your question of exactly what is the NO concentration at the alveolar level, you could look at it a couple of ways. You have a short bolus of gas going in at a set flow rate of 10 L/min out of the device. If the patient is inspiring at 40 L/min, that bolus is going to be diluted by three-fourths, from 100 ppm to 25 ppm. Don't forget this is an open system. If the patient is breathing fast, high tidal volumes, high flow rate, concentration is going to change. Again, I don't think concentration is the most important factor.

Hess: If I could just interject one thing. A point that you made that I really liked is that maybe it's not the concentration that's important, maybe we should be thinking about how many micro-moles of NO, for example, that the patient is breathing.

Gerlach: I once again want to ask you for the target parameters, P_{aO_2} and pulmonary artery pressure, if these are really the ideal parameters to define responders and nonresponders. You showed that the second patient definitely had no change in the pulmonary artery pressure, but as I remember, he had a change in the cardiac output. He was increasing, and, of course, if he once was on the decreasing part of the Frank-Starling curve, and he's improving now with the cardiac output, he will not show a decrease in pulmonary artery pressure. The second part is the P_{aO_2} and mixture of oxygen. We all know that when we're dealing with ARDS patients that after a while if the patient improves, then you have, let's say, 300 mm Hg with 100% oxygen. If you take the NO off, sometimes you have 100, which looks like a very big effect, but it's the same effect as if you have an increase from 55 to 65, if you take the oxygen content, for instance. So the question is whether you're blinding yourself if you just add a little bit of oxygen, just to keep the level up, and then of course see a very big change in the P_{aO_2}. But, in terms of the content of oxygen, it's probably the same. I don't know. If you recalculate that . . .

Channick: Those are excellent points. Obviously you can look at the numbers and then get down to the same question: What constitutes a favorable response? Anyone could pick a number and say that constitutes a favorable response. The question again, in these chronic patients, is what happens over time? I think we're looking at it a little bit differently. Like the patients with idiopathic pulmonary fibrosis. Yes, you could say the P_{aO_2} is going up, but why not just give them a little more oxygen and not give them NO? All I can tell you is that I think that it's doing other things than just raising oxygen in a patient like that: the improvement in pulmonary hypertension, although it may not be huge, coupled with the improvement in the P_{aO_2}, coupled with the improved exercise tolerance. You're looking at it as a whole. I don't know how you define a favorable response. In PPH patients, I think it's even more complicated, because, again, you're looking at what's clinically significant. It depends on how sick they are to begin with. For example, if you start at a pulmonary artery systolic pressure of 120 mm Hg and you drop by 20%, you're still pretty "sick" if you look at the numbers. But if you're starting at 40 mm Hg and drop to 36 mm Hg, even though this is less than 20%, the patient might still have a favorable outcome.

Pearl: Studying agents with disease-modifying activity is very difficult. For primary pulmonary hypertension, prostacyclin very clearly has disease modifying activity, but we know that we need to use doses which are at the limit that patients tolerate without significant adverse effects. If we use doses half that amount, we probably would not see benefit. Do we have any way of knowing how much NO we should give, and are there patients in whom, if they don't respond, we should just double it chronically?

Channick: No, I have no idea. That's a great question. But it can only be answered with large numbers of patients, because in this patient population, we're looking at responses that are very gradual. There's no way to look at an acute dose response curve.

Pearl: In the patients who have either had disease progression or have started to lose their response to NO, have you tried putting them on higher doses for a period of time?

Channick: We have, actually. I'm not convinced that has made a difference. But if I were to design a study, say a Phase 2 study, I would clearly have a low-dose group and a high-dose group to try to figure that out.

Hess: Would you have a placebo group?

Channick: One of the problems is how do we design an outpatient study, at least for primary pulmonary hypertension. For something like idiopathic pulmonary fibrosis, it would be very easy, because you have no other treatment, so a conventional or "placebo" group would be very acceptable. For primary pulmonary hypertension, you have prostacyclin, an approved drug, which makes it more complicated. If you didn't have prostacyclin, I'd feel very comfortable having a placebo group, because there's just no data to support that NO is going to have great efficacy in primary pulmonary hypertension. This is a dilemma I face when I'm putting patients into this protocol. We have one approved drug that's been shown to improve mortality in primary pulmonary hypertension. You obviously can't encourage a patient to go into an experimental protocol with NO and deny them this approved therapy. So, we've really been limited to people who for some reason can't get or don't want prostacyclin. So you're designing a study, you have to have some way to include prostacyclin; possibly have a rescue arm that gets prostacyclin, or study a less sick patient population so you can safely do a six-month trial without losing patients.

Gerlach: Are there any reports of adverse effects such as dizziness, or headaches such as have been reported from awake persons when they accidentally inhaled high concentrations of NO?

Channick: One patient complained of some nasal irritation (nosebleeds) which, of course, can occur with oxygen therapy. But the other patients had no complaints referable to the nose, headaches, or any systemic complaints that we felt were due to this therapy.

Listing and Reviews of Books and Other Media. Note to publishers: Send review copies of books, films, tapes, and software to Respiratory Care, 600 Ninth Avenue, Suite 702, Seattle WA 98104.

Books, Films, Tapes, & Software

Pulmonary Pathophysiology—The Essentials, 5th ed, John B West MD PhD DSc. Soft-cover, illustrated, 198 pages. Baltimore: Williams & Wilkins; 1997. $29.00.

Dr John B West is an established expert in the field of pulmonary physiology. This book is written as a companion book to **Respiratory Physiology—The Essentials**, 5th edition (Williams & Wilkins, 1995), in which he provides the classic description of the physiology of the normal lung. In contrast, **Pulmonary Pathophysiology—The Essentials** describes pulmonary physiology and pulmonary function in the diseased lung. The goal of this book is to help apply the understanding of pulmonary physiology in the normal lung to the diseased lung, and thus bridge the gap between preclinical basic sciences and clinical sciences in medical education. The book is broken down into 3 parts (10 chapters). Since the last edition of this book, published in 1992, some significant changes have occurred in understanding the pathophysiology of certain disease processes and treatments; these innovations are discussed in this edition, including brief discussions of the pathogenesis of asthma, emphysema, and pulmonary edema. Modifications have also been made in the sections describing peak expiratory flow rates, closing volume, airway resistance, bronchoactive drugs for the treatment of asthma, cystic fibrosis, mechanical ventilation, and normal values of pulmonary function tests.

The intended audience is primarily "medical students in their second and subsequent years," but also includes "physicians (anesthesiologists and cardiologists) and paramedical personnel (including intensive care personnel and respiratory therapists)" who encounter patients with respiratory problems. The author assumes that those reading this book have been exposed to the basic pathology of the lung and have an understanding of the normal physiology of the lung. However, basic concepts of physiology and pathology are reviewed in the discussion of the disease process and references are given where further explanations and details can be found (often in Dr West's **Respiratory Physiology—The Essentials**, 5th edition). Sections of his book that are particularly well-written and organized, like the chapters on ventilation, gas exchange and obstructive diseases, could stand alone and be helpful for those with less background in physiology and pathology.

Part One, "Lung Function Tests and What They Mean," is made up of 3 chapters. Chapter 1, "Ventilation," covers basic spirometry with interpretation of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio in relation to obstructive and restrictive ventilatory patterns. Additional topics covered include forced expiratory flow (FEF 25–75%), flow-volume curve, peak expiratory flow rate (PEFR), single breath nitrogen test, and closing volume. The author wrote a particularly clear and concise discussion of dynamic compression of airways during exhalation and closing volume, subjects that often create significant confusion for students of pulmonary physiology. These concepts are then referred to in later chapters to paint a clear picture of the manifestations of air flow obstruction in the abnormal lung. Omitted in this first chapter is a discussion of or a reference to normal spirometry values. Chapter 2, "Gas Exchange," describes arterial blood gas interpretation and diffusing capacity. The topic of gas exchange is quite complex and can be very difficult to simplify. Dr West does an excellent job simplifying this subject by limiting his discussion only to the most essential elements. This brevity, however, may lead some readers to have many questions that are beyond the scope of this book, but adequate references are given. Dr West clearly delineates the causes of hypoxia, discussing the shunt equation and ventilation-perfusion ratio (V/Q) mismatch; however, the description of V/Q mismatch would benefit from some simple illustrations. Interpretation of acid-base status is very limited, but does give enough detail for understanding application of concepts in later chapters. Chapter 3, "Other Tests," covers such diverse topics as static lung volumes, lung compliance, airway resistance, assessment of ventilatory response to oxygen and carbon dioxide, and exercise testing. Dr West also briefly describes what is known about dyspnea. The chapter does not flow very well because of the divergent topics discussed, but each individual topic is clearly defined and discussed.

Part Two, "Function of the Diseased Lung," includes 4 chapters and describes different lung diseases and how they relate to pulmonary physiology. Chapter 4 gives a clear and well-organized description of obstructive diseases and is the best chapter of the book. The chapter links pathology, clinical presentation, and pulmonary physiology extremely well, covering chronic bronchitis, emphysema, chronic obstructive pulmonary disease, asthma, and localized airway obstruction. Chapter 5 tackles the subject of restrictive diseases, starting with a nice description of the pathology of interstitial fibrosis. Dr West uses diffuse interstitial pulmonary fibrosis as the main clinical example. Other diseases causing restrictive defects are also briefly discussed, along with pleural disease and chest wall abnormalities. Given the breadth of this subject matter, this chapter was nicely condensed. Chapter 6, "Vascular Diseases," starts out by describing how pulmonary edema fluid is formed, hydrostatic and nonhydrostatic. The remainder of the chapter addresses pulmonary embolism and pulmonary hypertension. Interestingly, in the discussion of deep venous thrombosis and pulmonary embolism, the author never mentions the use of duplex ultrasound, one of the main diagnostic tests employed now to diagnose deep venous thrombosis. Chapter 7, "Environmental and Other Diseases," ensures that a breadth of topics is discussed, including a nice discussion of particle deposition in the lung and cilial function.

Part Three, "Function of the Failing Lung," devotes a chapter each to describing respiratory failure, oxygen therapy, and mechanical ventilation. In Chapter 8, Dr West clearly organizes the different types of respiratory failure, then in more detail describes the more common clinical entities and summarizes the chapter with management. The chapter on oxygen therapy does a good job at delineating different responses to oxygen and briefly describes oxygen delivery, but never mentions how oxygen content is affected by saturation and arterial oxygen tension (P_{aO_2}). The author then briefly describes several methods of oxygen administration and the hazards of oxygen therapy, such as CO_2 retention, oxygen toxicity (with no mention of the current controversy concerning its importance), and absorption atelectasis. The description of absorption atelectasis is particularly well done. The chapter on mechanical ventilation inadequately defines and describes different modes of ventilation, but has a good discussion of the effects of positive end-expiratory pressure (PEEP) and positive intrathoracic pressure on oxygenation, physiologic dead space, and hemodynamics.

The appendices provide useful information, including the equation for conversion of gas volumes using body temperature and pressure, saturated (BTPS), and reference values for white nonsmoking males and females. It also contains a list of references that is appropriately abbreviated and contains good resources for more detailed information. The book also contains a list of questions with answers pertaining to each of the book's chapters. The index appears useful and complete.

Overall, this book is clearly organized and well-written. Dr West did an excellent job integrating both pathology and physiology of different disease states in the lung. The figures and photomicrographs are very instructive and additive to the text. I did find a few errors in description of different diseases. For example, in Chapter 7, psittacosis is erroneously described as a rickettsial disease; *Chlamydia psittaci* is an obligate intracellular bacteria in the order Chlamydiales and the family Chlamydiaceae. Chapter 7 also states that patients with acquired immunodeficiency syndrome (AIDS) often get lung infections with cytomegalovirus. This statement, while true, is misleading, for though cytomegalovirus often may be cultured from bronchoalveolar lavage fluid, cytomegalovirus pneumonitis is uncommon. The author also states that an abnormally high sweat sodium level confirms the diagnosis in children with cystic fibrosis. This should read sweat chloride. In the recent consensus statement by Rosenstein et al (*Journal of Pediatrics*, April 1998; 132:4:589–595), sweat sodium levels can be increased in diseases other than cystic fibrosis and should not be used. He also groups surgical thromboembolic disease in the discussion of primary pulmonary hypertension (the two being very distinct clinical entities).

The strengths of this book are that it links disease states to pulmonary physiology, ie, the effect of PEEP on V/Q mismatch, shunt, and physiologic dead space in acute respiratory distress syndrome. The weaknesses of the book stem from Dr West's attempt to cover too many clinically distinct entities, giving very little discussion to each. This is particularly problematic at the end of Chapter 7 where asbestosis, other pneumoconioses, malignant diseases, infectious diseases, AIDS, and cystic fibrosis are all discussed in 6 pages.

In conclusion, Dr West did an excellent job explaining the function of the diseased lung and did indeed bridge the gap between basic science and clinical science. This book would be an excellent review book for physicians and an excellent companion book for medical students who have already had or are currently taking pulmonary physiology. The book is also appropriate for those paramedical personnel with a background in pulmonary physiology.

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UpToDate in Pulmonary Disease and Critical Care Medicine, Version 6.3, Steven E Weinberger MD, Editor-in-Chief (Burton D Rose MD, Series Editor). Wellesley, MA: UpToDate Inc; October 1998. Annual subscription with updates every 4 months, $495.00.

System Requirements: Windows: MS Windows version 3.1 or higher. A 486/25 or Pentium processor is preferred. 8 MB of free space on the hard drive and a minimum of 16 MB of RAM. Macintosh: An Apple Macintosh computer with 68040 or Power PC processor. 8 MB of free space on the hard drive. System 7.0 or higher and a minimum of 16 MB of RAM. A compatible CD-ROM drive is required of all systems.

If you have ever tried to answer a clinically related question in 15 seconds or less, this is the resource for you. **UpToDate** is a comprehensive educational resource for pulmonary and critical care, as well as many other medicine subspecialties, available as a CD-ROM subscription. **UpToDate** combines textbook knowledge, current literature, American Thoracic Society guidelines, treatment recommendations, and self-education tools into one well-indexed reference that is easily installed in your computer and even easier to use. It could easily replace the stacks of journals, rows of textbooks, and time-consuming modem links that you currently use to find answers to clinical questions. Every 4 months, you receive an updated CD-ROM in the mail and toss out your old one. What could be easier? And if you are worried that finding your CD may take longer than 15 seconds, the whole disk can be loaded onto your hard drive (at the expense of a lot of memory.)

Consider **UpToDate** as a textbook that is updated 3 times per year. Pulmonary and critical care "chapters" are indexed separately and called "topic cards." A nationally recognized leader in the field authors each topic card. Burton D Rose of Harvard Medical School is the Editor-in-Chief of the entire **UptoDate** series, which also includes subspecialty texts in cardiology, endocrinology, nephrology, gastroenterology, and rheumatology, and ultimately will cover all of internal medicine. All available subspecialties as well as the first 13 chapters of Dr Rose's textbook, **Clinical Physiology of Acid-Base and Electrolyte Disorders** are included on each CD-ROM. As a pulmonary specialist, I enjoyed being able to quickly find the answer to questions outside my field, which could not be found in the books and journals I keep.

When you open the **UpToDate** program, a crisply laid-out window appears that includes the list of subspecialty areas, a box for beginning your search, and a "Did you know?" tip box (described below). If you click on a subspecialty, a table of contents for that subject appears. A topic can then be selected from there. Alternatively, you can type in a key word in the search box, and a list of possible topics appears. Complex searches can be done using topic modifiers and cross-references. For example, if you wanted to learn about the use of anti-leukotriene agents in asthma, you enter the term, "asthma," modify it by clicking on "treatment," and cross-reference it with "leukotrienes." You could also open the entire National Asthma Education Project guidelines and search within the document for anti-leukotriene agents.

The search mechanism was improved from version 6.2 to the 6.3 version, allowing for more selective searches. The search is now more likely on the first try to hone in on the topic you are seeking. There is, however, a consistent minor glitch that appears to originate from the search mechanism's reliance on the alphabet. For example, when you search for ACE inhibitors, topic lists for acetazolamide will also be found. In the end, though, it is probably preferable to have a search engine that is more inclusive, rather than less.

When the topic card is opened, a textbook-like window appears with accompanying figures, tables, color photos, and video clips. The author and the date the topic card was prepared appears at the top. Embedded in the well-written text are highlighted links to other topic cards, so that moving from topic to topic is as easy as a click of the mouse. Each topic card is fully referenced, and with a click of the mouse, the reference's MEDLINE abstract appears in full. Similarly, drug names are highlighted in the text as well; with a click, a full drug information data sheet appears. An outline of each topic card can be viewed at any time, and you can jump directly to another section of the topic card from the outline. If you are averse to studying from a computer screen, topic cards can be printed out in full, complete with references. The only disadvantage of printing out the entries is that figures and tables are not printed automatically. You can, however, go back to the text, open the figure or table, and print it separately.

The figures and tables are clear and in color. The graphs and tables are adapted and redone for the program, not just scanned into the text. Chest radiographs and computed tomography scans are reproduced with wonderful clarity (on a high-resolution computer monitor). Histology and microbiology slides are not as uniformly good, but superior to the average textbook. Graphs and tables print well. Radiographs, pathology, and photographs print less well and are dependent on the quality of the printer. There are also short video and audio clips that can be played. The most useful ones were in the cardiology section and included echocardiograms and angiograms. The video clips in the pulmonary section, eg, a movie of a laser resection of an endobronchial carcinoid tumor, were fun to watch but educationally superfluous.

Although targeted for physicians, the program has a variety of learning tools useful to most every practitioner in the field of medicine, including respiratory therapists and medical students. The "Did you know?" tip box appears every time the program is opened. It states a fact that is current and written to pique your interest. It then allows you to click directly to the topic card that describes it in full. For example, while reviewing the software, I learned about a transfusion-transferred virus that was not hepatitis G (I then clicked to learn about hepatitis G) and that alendronate was almost as good as estrogen in preventing osteoporosis.

The search tool bar allows you to go directly to learning aids. "Recent Cards" can be clicked to show the topics added in the last 4 months. "Lists of Pictures" allow you to go directly to collections of radiographs, histology slides, and photos, which can be reviewed as a group. There is also an electrocardiograph (ECG) self-teach program with groups of ECGs divided into basic, intermediate, and advanced levels. An ECG is displayed, you take your time interpreting it, then click on the field and a caption appears which interprets the ECG and points to salient features.

The software can be used as a teaching tool as well. Topic cards and figures can be printed or put into other software packages, such as Microsoft Word or PowerPoint, to make educational handouts or slides. Audiograms of heart murmurs can be reviewed by individuals or by groups. The publishers encourage use of their material in this manner but do remind you of copyright infringement if the entire contents were to be distributed. There are built-in calculators that will find alveolar-arterial oxygen ($P_{(A-a)O_2}$). differences or shunt fractions by just plugging in the numbers. Although designed for clinical use, it would be more useful for setting up examples for students and showing what happens when different variables are changed.

Continuing medical education credit can be earned by using the software. The **UpToDate** program keeps a log of the topic cards you read, the searches you perform, and the hours you use the program. The log can be downloaded and sent directly to the **UpToDate** publisher who will forward the number of hours to the American Medical Association.

Although I encountered no technical difficulties, the promotional brochure describes the technical help desk as friendly and efficient, so I decided to call anyway. The telephone was picked up within 2 rings by a real human, not a voice mail menu. I mentioned that I had just installed the CD-ROM and the voice volunteered that about 5% of the PC users were experiencing a glitch. He first apologized for not being the usual support staff since it was a national holiday, then immediately faxed me clearly written instructions for fixing the problem that I did not have. Later I learned that it was Dr Rose himself who had been so friendly, efficient, and genuinely helpful.

Overall, **UpToDate** is a comprehensive reference tool for most areas of internal medicine designed to be used to answer questions easily. It also is an excellent educational tool. There is evidence that the publisher is responsive to the user's needs (eg, the new search methods). The expectation is that the software will continue to evolve, especially video and audio clips. By design, the product is a dynamic assemblage of information that answers a need in a field undergoing an information explosion. The cost, $495.00 per year's subscription, is daunting but justified if you add up the cost of the minimum of 10 reference books and 20 journal subscriptions that this could replace. Nonphysicians may have more difficulty justifying the expense. The most difficult part of answering interesting clinical questions should now be turning on your computer.

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The Survey Kit, Arlene Fink, Series Editor. Vol 1, **The Survey Handbook,** Arlene Fink (144 pages); Vol 2, **How to Ask Survey Questions**, Arlene Fink (120 pages); Vol 3, **How to Conduct Self-Administered and Mail Surveys**, Linda B Bourque and Eve P Fielder (240 pages); Vol 4, **How to Conduct Interviews by Telephone and in Person,** James H Frey and Sabine Mertens Oishi (184 pages); Vol 5, **How to Design Surveys**, Arlene Fink (88 pages); Vol 6, **How to Sample Surveys,** Arlene Fink (88 pages); Vol 7, **How to Measure Survey Reliability and Validity,** Mark S Litwin (88 pages); Vol 8, **How to Analyze Survey Data,** Arlene Fink (112 pages); Vol 9, **How to Report on Surveys,** Arlene Fink (112 pages). Soft-cover books in a cardboard case. Thousand Oaks, CA: Sage Publications Inc; 1997. $144.00.

The Survey Kit is intended as a resource for anyone without a statistical background who needs to design or administer a survey. It is suitable both for students and for professional researchers. The expense of running a survey has a strong impact on which survey designs are viable for any given project; in order to make informed decisions about what type of survey to use, a researcher must have some understanding of both the practical and theoretical aspects of survey design. This corresponds to the 2 main goals of the kit: to provide practical information about setting up and running a survey, and to give an easy-to-read discussion of survey design and analysis. Though many of the examples used are from the health sciences, the kit is not specifically tailored to any particular field. It consists of 9 short volumes, beginning with the introductory Volume 1. Volumes 2, 3, 4, and 9 cover the practical side of survey administration, while Volumes 5, 6, 7, and 8 discuss how to design and analyze a valid survey.

The Survey Handbook provides an overview of the main aspects of survey design. After a general introduction to surveys, it gives a concise description of sampling methods, survey types, and the issues of reliability and validity. This is followed by a discussion of the nuts and bolts of organizing and running a survey. The material in this volume is a well-organized introduction to surveys for the reader who is not mathematically oriented. This volume serves as a summary for the rest of the kit; it avoids mathematics and leaves deeper discussion for the other volumes.

How to Ask Survey Questions provides guidance on how to design questions so that they draw out the desired information. If a question is frequently misinterpreted or perceived to be threatening, then it may not provide useful data to the researcher. The art of asking clear, concrete questions is analyzed, along with a discussion of question types (categorical, ordinal, and numerical) and when each is appropriate. **How to Conduct Self-Administered and Mail Surveys** and **How to Conduct Interviews by Telephone and in Person** are practical how-to guides for running a survey, complete with checklists, sample letters, and scripts, and even a guide for training interviewers. Methods for effectively communicating survey results both orally and in writing are discussed in **How to Report on Surveys**. A researcher who is a novice in the field of survey methods will find these volumes a useful source of practical advice and guidelines for conducting a survey.

How to Design Surveys and **How to Sample in Surveys** describe common survey designs and sampling methods. Potential problems with statistical validity are presented, and a bit of mathematics is introduced. The information in these volumes enables a researcher to understand a statistician's main concerns when examining a survey design.

A concise introduction to statistical topics relevant to surveys is given in **How to Measure Survey Reliability and Validity** and **How to Analyze Survey Data**. Although a complete discussion of this field is beyond the scope of this kit, these volumes provide both a discussion of some methods that are commonly used to analyze survey data and a basic introduction to statistics. Since the authors strive for readability, the mathematics and statistics are kept at an introductory level. While one can find a similar introduction to statistics in many other texts, this kit stays in the context of survey design, which might make the topics clearer to less mathematically inclined readers.

The Survey Kit provides a useful how-to resource for the practical details of administering a survey and presents the basic concepts of survey design and analysis in a very accessible manner. Throughout the kit, many examples are provided to make the ideas concrete and clear.

This kit gives the researcher without a statistical background the ability to communicate clearly with statisticians and the tools to think critically about survey data.

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Self-Management of Asthma, No. 113, Lung Biology in Health and Disease, Harry Kotses PhD and Andrew Harver PhD, Editors. Hardcover, illustrated, 445 pages. New York: Marcel Dekker Inc; 1998. $175.00.

Self-Management of Asthma is a compilation dedicated to the behavioral side of asthma. Recent reports indicate that health care professionals are not doing an adequate job teaching patients to manage their own asthma. The numbers are dismal: few patients take their medication properly, know what their medication is for, or know how to treat exacerbations of their asthma. This book suggests strategies for overcoming the current state of affairs.

The editors have gone to great lengths to provide a well-balanced view of the topic. They have covered both the medical and psychological management of patients with asthma and their families. They present a clear picture of the reasons patients are not compliant with their asthma therapy. The medical field as a whole can learn a great deal from this book. We are given a challenge to improve the current statistics and help our patients learn to manage their own disease. We all know intellectually that we can not take care of our patients once we send them home. It is up to the patients and their families to do this. However, we are responsible for providing the tools and the information for them to do so successfully. This book explains the scope of the problem and offers suggestions for solutions that will improve asthma care in this country.

This volume is intended for general practitioners, asthma specialists, and patients. The goal is to encourage physicians to institute self-management programs to help treat the increasing asthma population. The benefit, in the authors' view, will be mostly to the patient. However, teaching health care professionals how to motivate patients to accept responsibility for their own health will only strengthen our medical system as a whole.

Each chapter in the book has a bibliography to help with further individual research. The index at the back and the table of contents make it easy to find specific topics. The references are exhaustive and cover early articles to the most recent. I was pleased that there were few typographical errors; the editors did an excellent job.

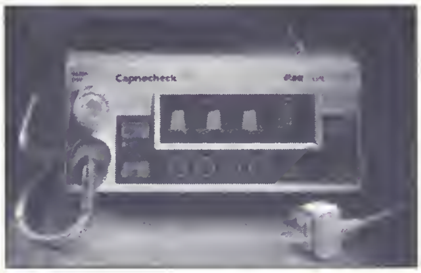
I would recommend this book to anyone who is interested in learning why patients do not comply with the directions we give them. But most importantly, this book outlines strategies for health professionals to help patients manage their own asthma.

Kathy Boyle MS RRT
Respiratory Care Services
Arkansas Children's Hospital
Little Rock, Arkansas

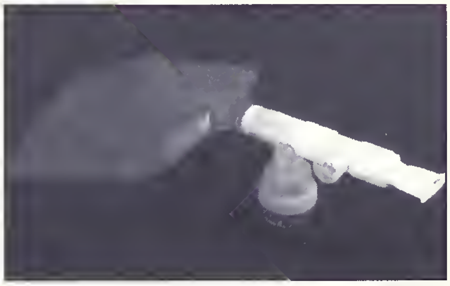
News releases about new products and services will be considered for publication in this section. There is no charge for these listings. Send descriptive release and glossy black and white photographs to RESPIRATORY CARE, New Products & Services Dept, 11030 Ables Lane, Dallas TX 75229-4593. The Reader Service Card can be found at the back of the Journal.

New Products & Services

Pen Sound Simulator. Astro-Med Inc's Grass Instrument Division announces the release of a newly designed "pen sound simulator" for EEG and PSG systems. A company press release says the unit, Model PSS-162, is designed to produce the audible sounds of a traditional direct-writing oscillographic recorder while the silent Grass Heritage digital EEG and PSG systems display and capture data. According to the company, six channels of conditioned analog signals from the EEG or PSG can be interfaced to the simulator which generates a composite audio signal to drive its powered speaker system. Grass Instrument Division says the pen sound simulator is particularly useful during multiple patient or semi-unattended recording. For more information from Astro-Med Inc's Grass Instrument Division, circle number 183 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/.



Capnograph. BCI International introduces the Capnocheck® DualStream™ Capnograph. A BCI press release says the device combines mainstream and sidestream sampling technology into a single, stand-alone system and that it was designed with ease of use in mind, reaching full operating specification in 45 seconds; self-calibrating 30 times per second; and withstanding excessive patient secretions while providing accurate CO_2 values. BCI says the monitor and alarm setups are easy to understand and that the display has noted high visibility. For more information BCI International, circle number 184 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/.



Nebulizer Delivery System. Piper Medical introduces a new nebulizer delivery system, the AeroTee. According to a company press release, the device delivers 50% more medication than a conventional nebulizer tee configuration. Piper Medical says the AeroTee functions by storing aerosol produced by the nebulizer during exhalation for delivery to the patient on the subsequent inhalation. Company literature also says the device uses a laminar purging technique that maximizes the delivery of aerosol to the patient while keeping the volume of rebreathed gas down to the level of a conventional nebulizer tee. For more information from Piper Medical, circle number 185 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/.

Improved Monitoring System. Spacelabs Burdick Inc has added new features to its Vision Premier™ Holter Monitoring System. According to the company, the Vision Premier™ presents comprehensive clinical data with sharp clarity and accuracy and provides unlimited access to data with its four data communications possibilities: a built-in fax/modem, "PDF" file transfer option, network compatibility, and remote satellite operations. Spacelabs Burdick literature says new features include: analysis and review capability of up to 48-hour recordings from analog or digital recorders with programmable report formats, network support of the latest versions of NT, Ethernet, and Novell, expanded programmability of Heart Rate Variability Analysis for Frequency Domain calculations, and a built in CD drive for backing up old Holter studies for off-line storage. For more information from Spacelabs Burdick Inc, circle number 186 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting
by health professionals of adverse
events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291 Expires: 4/30/96
See OMB statement on reverse

FDA Use Only (Reap Care)

Triage unit
sequence #

A. Patient information

1. **Patient identifier**
In confidence

2. **Age at time of event:** ____
or
Date of birth:

3. **Sex**
☐ female
☐ male

4. **Weight**
____ lbs
or
____ kgs

B. Adverse event or product problem

1. ☐ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

Outcomes attributed to adverse event
(check all that apply)

☐ death ____ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

Date of event (mo/day/yr)

4. **Date of this report** (mo/day/yr)

Describe event or problem

Relevant tests/laboratory data, including dates

Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, if known)
#1 ____
#2

2. **Dose, frequency & route used**
#1 ____
#2

3. **Therapy dates** (if unknown, give duration)
from/to (or best estimate)
#1 ____
#2

4. **Diagnosis for use** (indication)
#1 ____
#2

5. **Event abated after use stopped or dose reduced**
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. **Lot #** (if known)
#1 ____
#2

7. **Exp. date** (if known)
#1 ____
#2

8. **Event reappeared after reintroduction**
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. **NDC #** (for product problems only)
– –

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

D. Suspect medical device

1. **Brand name**

2. **Type of device**

3. **Manufacturer name & address**

4. **Operator of device**
☐ health professional
☐ lay user/patient
☐ other: ____

5. **Expiration date** (mo/day/yr)

6.
model # ____
catalog # ____
serial # ____
lot # ____
other #

7. **If implanted, give date** (mo/day/yr)

8. **If explanted, give date** (mo/day/yr)

9. **Device available for evaluation?** (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. **Name & address**

phone #

2. **Health professional?**
☐ yes ☐ no

3. **Occupation**

4. **Also reported to**
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or **FAX to:**
1-800-FDA-0178

DA Form 3500 1/96)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

• 1-800-FDA-0178	to FAX report
• 1-800-FDA-7737	to report by modem
• 1-800-FDA-1088	to report by phone or for more information
• 1-800-822-7967	for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please do NOT return this form to either of these addresses.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

FDA Form 3500-back

Please Use Address Provided Below – Just Fold In Thirds, Tape and Mail

Department of
Health and Human Services
Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES
OR APO/FPO

BUSINESS REPLY MAIL

FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE, MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

American Association for Respiratory Care

MEMBERSHIP APPLICATION

Please read the eligibility requirements for each of the classifications in the right-hand column, then complete the applicable section. All information requested below must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application on reverse side and type or print clearly. Processing of application takes approximately 15 days.

- ☐ Active
- Associate
    - ☐ Foreign
    - ☐ Physician
    - ☐ Industrial
- ☐ Special
- ☐ Student

Last Name ______________________________

First Name ______________________________

Social Security No. ______________________________

Home Address ______________________________

City ______________________________

State ____________ Zip __ __ __ __ __ — __ __ __ __

Phone No. (______) ______________________________

Primary Job Responsibility (check one only)

- ☐ Technical Director
- ☐ Assistant Technical Director
- ☐ Pulmonary Function Specialist
- ☐ Instructor/Educator
- ☐ Supervisor
- ☐ Staff Therapist
- ☐ Staff Technician
- ☐ Rehabilitation/Home Care
- ☐ Medical Director
- ☐ Sales
- ☐ Student
- ☐ Other, specify ____________________

Type of Business

- ☐ Hospital
- ☐ Skilled Nursing Facility
- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Educational Institution
- ☐ Manufacturer or supplier
- ☐ Other, specify ____________________

Date of Birth (optional) ____________ Sex (optional) ________

U.S. Citizen? ____ Yes ____ No

Have you ever been a member of the AARC? ____________________

If so, when? From ____________ to ____________

Preferred mailing address: ☐ Home ☐ Business

For office use only

FOR ACTIVE MEMBER

An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care, OR (3) holds a credential issued by the NBRC. An individual who is an AARC Active Member in good standing on December 8, 1994, will continue as such provided his/her membership remains in good standing.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment ______________________________

Address ______________________________

City ______________________________

State ____________ Zip __ __ __ __ __ - __ __ __ __

Phone No. (______) ______________________________

Medical Director/Medical Sponsor ______________________________

FOR ASSOCIATE OR SPECIAL MEMBER

Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment ______________________________

Address ______________________________

City ______________________________

State ____________ Zip __ __ __ __ __ - __ __ __ __

Phone No. (______) ______________________________

FOR STUDENT MEMBER

Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

School/RC Program ______________________________

Address ______________________________

City ______________________________

State ____________ Zip __ __ __ __ __ - __ __ __ __

Phone No. (______) ______________________________

Length of program

☐ 1 year ☐ 4 years

☐ 2 years ☐ Other, specify ____________

Expected Date of Graduation *(REQUIRED INFORMATION)*

Month ________ Year ________

AARC

American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • (972) 243-2272 • Fax (972) 484-2720

American Association for Respiratory Care MEMBERSHIP APPLICATION

Demographic Questions

We request that you answer these questions in order to help us design services and programs to meet your needs.

Check the Highest Degree Earned

- ☐ High School
- ☐ RC Graduate Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorate Degree

Number of Years in Respiratory Care

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

Job Status

- ☐ Full Time
- ☐ Part Time

Credentials

- ☐ RRT
- ☐ CRT
- ☐ Physician
- ☐ CRNA
- ☐ RN
- ☐ LVN/LPN
- ☐ CPFT
- ☐ RPFT
- ☐ Perinatal/Pediatric

Salary

- ☐ Less than $10,000
- ☐ $10,001-$20,000
- ☐ $20,001-$30,000
- ☐ $30,001-$40,000
- ☐ $40,000 or more

PLEASE SIGN

I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is cause for rejection or expulsion.

A yearly subscription to RESPIRATORY CARE journal and *AARC Times* magazine includes an allocation of $11.50 from my dues for each of these publications.

NOTE: Contributions or gifts to the AARC are not tax deductible as charitable contributions for income tax purposes. However, they may be tax deductible as ordinary and necessary business expenses subject to restrictions imposed as a result of association lobbying activities. The AARC estimates that the nondeductible portion of your dues — the portion which is allocable to lobbying — is 26%.

Signature ____________________

Date ____________________

Membership Fees

Payment must accompany your application to the AARC. Fees are for 12 months. (NOTE: Renewal fees are $75.00 Active, Associate-Industrial or Associate-Physician, or Special status; $90.00 for Associate-Foreign status; and $45.00 for Student status).

☐ Active	$ 87.50
☐ Associate (Industrial or Physician)	$ 87.50
☐ Associate (Foreign)	$102.50
☐ Special	$ 87.50
☐ Student	$ 45.00
TOTAL	$__________

Specialty Sections

Established to recognize the specialty areas of respiratory care, these sections publish a bi-monthly newsletter that focuses on issues of specific concern to that specialty. The sections also design the specialty programming at the national AARC meetings.

☐ Adult Acute Care Section	$15.00
☐ Education Section	$20.00
☐ Perinatal-Pediatric Section	$15.00
☐ Diagnostics Section	$15.00
☐ Continuing Care-Rehabilitation Section	$15.00
☐ Management Section	$20.00
☐ Transport Section	$15.00
☐ Home Care Section	$15.00
☐ Subacute Care Section	$15.00
TOTAL	$__________

GRAND TOTAL = Membership Fee plus optional sections $__________

- ☐ Total Amount Enclosed/Charged $__________________
- ☐ Please charge my dues (see below)

To charge your dues, complete the following:

- ☐ MasterCard
- ☐ Visa

Card Number

__ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

Card Expires ______/______

Signature ______________________________

Mail application and appropriate fees to:
American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • [972] 243-2272 • Fax [972] 484-2720

call for abstracts

1999 RESPIRATORY CARE OPEN FORUM

The American Association for Respiratory Care and its science journal, Respiratory Care, invite submission of brief abstracts related to any aspect of cardiorespiratory care. The abstracts will be reviewed, and selected authors will be invited to present posters at the Open Forum during the AARC International Respiratory Congress in Las Vegas, Nevada, December 13–16, 1999. Accepted abstracts will be published in the November 1999 issue of Respiratory Care. Membership in the AARC is not required for participation. All accepted abstracts are automatically considered for ARCF research grants.

SPECIFICATIONS—READ CAREFULLY!

An abstract may report **(1) an original study, (2) the evaluation of a method, device or protocol, or (3) a case or case series.** Topics may be aspects of adult acute care, continuing care/rehabilitation, perinatology/pediatrics, cardiopulmonary technology, or health care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal. The abstract is the only evidence by which the reviewers can decide whether the author should be invited to present a poster at the Open Forum. Therefore, *the abstract must provide all important data, findings, and conclusions.* Give specific information. Do not write general statements, such as "Results will be presented" or "Significance will be discussed."

ESSENTIAL CONTENT ELEMENTS

Original study. Abstract *must* include (1) Background: statement of research problem, question, or hypothesis; (2) Method: description of research design and conduct in sufficient detail to permit judgment of validity; (3) Results: statement of research findings with quantitative data and statistical analysis; (4) Conclusions: interpretation of the meaning of the results.

Method, device, or protocol evaluation. Abstract *must* include (1) Background: identification of the method, device, or protocol and its intended function; (2) Method: description of the evaluation in sufficient detail to permit judgment of its objectivity and validity; (3) Results: findings of the evaluation; (4) Experience: summary of the author's practical experience or a lack of experience; (5) Conclusions: interpretation of the evaluation and experience. Cost comparisons should be included where possible and appropriate.

Case report. Abstract *must* report a case that is uncommon or of exceptional educational value and must include (1) Introduction: relevant basic information important to understanding the case. (2) Case Summary: patient data and response, details of interventions. (3) Discussion: content should reflect results of literature review. The author(s) should have been actively involved in the case and a case-managing physician must be a co-author or must approve the report.

FORMAT AND TYPING INSTRUCTIONS

Accepted abstracts will be photographed and reduced by 40%; therefore, the size of the original text should be *at least* 10 points. *Abstracts should be 400 words or less and may have 1 clear, concise table or figure.* A font like Helvetica or Geneva makes the clearest reproduction. The first line of the abstract should be the title in all capital letters. Title should explain content. Follow title with names of all authors (including credentials), institution(s), and location; underline presenter's name. Type or electronically print the abstract *single spaced in a single paragraph in the space provided on the abstract blank.* Insert only one letter space between sentences. Text submission on diskette is encouraged but must be accompanied by a hard copy. *Data may be submitted in table form, or a simple figure may be included provided it fits within the space allotted. No figure, illustration, or table is to be attached to the abstract form.* Provide all author information requested. A clear photocopy of the abstract form may be used. Standard abbreviations may be employed without explanation; new or infrequently used abbreviations should be spelled out on first use. Any recurring phrase or expression may be abbreviated, if it is first explained. Check the abstract for (1) errors in spelling, grammar, facts, and figures; (2) clarity of language; and (3) conformance to these specifications. An abstract not prepared as requested may not be reviewed. Questions about abstract preparation may be telephoned to the editorial staff of Respiratory Care at (972) 406-4667.

Early Deadline Allowing Revision. Authors may choose to submit abstracts early. Abstracts postmarked by April 2, 1999 will be reviewed and the authors notified *by letter only* to be mailed by May 7, 1999. Rejected abstracts will be accompanied by a written critique that should, in many cases, enable authors to revise their abstracts and resubmit them by the Final Deadline (June 11, 1999).

Final Deadline. The mandatory Final Deadline is June 11, 1999 (postmark). Authors will be notified of acceptance or rejection *by letter only.* These letters will be mailed by August 25, 1999.

Mailing Instructions. Mail (do not fax!) 2 clear copies of the completed abstract form, diskette (if possible), and a stamped, self-addressed postcard (for notice of receipt) to:

1999 Respiratory Care Open Forum
11030 Ables Lane
Dallas TX 75229-4593

submit your OPEN FORUM abstract electronically
visit www.rcjournal.com

1999 RESPIRATORY CARE OPEN FORUM Abstract Form

18.8 cm or 7.4"

13.9 cm or 5.5"

1. Title must be in all upper case (capital) letters, authors' full names and text in upper and lower case.
2. Follow title with all authors' names, including credentials (underline presenter's name), institution, and location.
3. Do not justify (ie, leave a 'ragged' right margin).
4. **Do not use type size less than 10 points.** (Do not exceed 400 words.)
5. All text and the table, or figure, must fit into the rectangle shown. (Use only 1 clear, concise table or figure.)
6. Submit 2 clean copies. This form may be photocopied if multiple abstracts are to be submitted.

Mail original & 1 photocopy (along with postage-paid postcard) to

1999 RESPIRATORY CARE OPEN FORUM
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Early Deadline is April 2, 1999 (postmark)

Final Deadline is June 11, 1999 (postmark)

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Corresponding Author If Different from Presenter

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RESPIRATORY CARE

Manuscript Preparation Guide

General Information

RESPIRATORY CARE welcomes original manuscripts related to the science and technology of respiratory care and prepared according to these Instructions and the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* [Respir Care 1997; 42(6):623-634]. Manuscripts are blinded and reviewed by professionals who are experts in their fields. Authors are responsible for all aspects of the manuscript and receive galleys to proofread before publication. Each accepted manuscript is copyedited so that its message is clear and it conforms to the Journal's style. Published papers are copyrighted by Daedalus Inc and may not be published elsewhere without permission.

Editorial consultation is available at any stage of planning or writing. On request, specific guidance is provided for all publication categories. To receive these Instructions and related materials, write to RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104, call (206) 223-0558, or fax (206) 223-0563.

Publication Categories & Structure

Research Article: A report of an original investigation (a study). It includes a Title Page, Abstract, Introduction, Methods, Results, Discussion, Conclusions, Product Sources, Acknowledgments, References, Tables, Appendices, Figures, and Figure Captions.

Evaluation of Device/Method/Technique: A description and evaluation of an old or new device, method, technique, or modification. It has a Title Page, Abstract, Introduction, Description of Device/Method/Technique, Evaluation Methods, Evaluation Results, Discussion, Conclusions, Product Sources, Acknowledgments, References, Tables, Appendices, Figures, and Figure Captions. Comparative cost data should be included wherever possible.

Case Report: A report of a clinical case that is uncommon, or was managed in a new way, or is exceptionally instructive. All authors must be associated with the case. A case-managing physician must either be an author or furnish a letter approving the manuscript. Its components are Title Page, Abstract, Introduction, Case Summary, Discussion, References, Tables, Figures, and Figure Captions.

Review Article: A comprehensive, critical review of the literature and state-of-the-art summary of a pertinent topic that has been the subject of at least 40 published research articles. Title Page, Outline, Introduction, Review of the Literature, Summary, Acknowledgments, References. Tables, Appendices, and Figures and Captions may be included.

Overview: A critical review of a pertinent topic that has fewer than 40 published research articles.

Update: A report of subsequent developments in a topic that has been critically reviewed in this Journal or elsewhere.

Point-of-View Paper: A paper expressing personal but substantiated opinions on a pertinent topic. Title Page, Text, References, Tables, and Illustrations may be included.

Special Article: A pertinent paper not fitting one of the foregoing categories may be acceptable as a Special Article. Consult with the Editor before writing or submitting such a paper.

Editorial: A paper drawing attention to a pertinent concern; it may present an opposing opinion, clarify a position, or bring a problem into focus.

Letter: A signed communication, marked "For publication," about prior publications in this Journal or about other pertinent topics. Tables and illustrations may be included.

Blood Gas Corner: A brief, instructive case report involving blood gas values—with Questions, Answers, and Discussion.

Drug Capsule: A mini-review paper about a drug or class of drugs that includes discussions of pharmacology, pharmacokinetics, and pharmacotherapy.

Graphics Corner: A brief case report incorporating waveforms for monitoring or diagnosis—with Questions, Answers, and Discussion.

Kittredge's Corner: A brief description of the operation of respiratory care equipment—with information from manufacturers and editorial comments and suggestions.

PFT Corner: Like Blood Gas Corner, but involving pulmonary function tests.

Cardiorespiratory Interactions. A case report demonstrating the interaction between the cardiovascular and respiratory systems. It should be a patient-care scenario; however, the case—the central theme—is the systems interaction. CRI is characterized by figures, equations, and a glossary. See the March 1996 Issue of RESPIRATORY CARE for more detail.

Test Your Radiologic Skill: Like Blood Gas Corner, but involving pulmonary medicine radiography and including one or more radiographs; may involve imaging techniques other than conventional chest radiography.

Review of Book, Film, Tape, or Software: A balanced, critical review of a recent release.

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Center main section headings on the page and type them in capital and small letters (eg, Introduction, Methods, Results, Discussion). Begin subheadings at the left margin and type them in capital and small letters (eg, Patients, Equipment, Statistical Analysis).

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Article in a journal carrying pagination throughout volume:

> Rau JL, Harwood RJ. Comparison of nebulizer delivery methods through a neonatal endotracheal tube: a bench study. Respir Care 1992;37(11):1233-1240.

Article in a publication that numbers each issue beginning with Page 1:

> Bunch D. Establishing a national database for home care. AARC Times 1991;15(Mar):61,62,64.

Corporate author journal article:

> American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33(11):1044-1046.

Article in journal supplement: (Journals differ in their methods of numbering and identifying supplements. Supply sufficient information to promote retrieval.)

> Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986; 89(3 Suppl):139S-143S.

Abstract in journal: (Abstracts citations are to be avoided. Those more than 3 years old should not be cited.)

> Stevens DP. Scavenging ribavirin from an oxygen hood to reduce environmental exposure (abstract). Respir Care 1990;35(11): 1087-1088.

Editorial in journal:

> Enright P. Can we relax during spirometry? (editorial). Am Rev Respir Dis 1993;148(2):274.

Editorial with no author given:

> Negative-pressure ventilation for chronic obstructive pulmonary disease (editorial). Lancet 1992;340(8833):1440-1441.

Letter in journal:

> Aelony Y. Ethnic norms for pulmonary function tests (letter). Chest 1991;99(4):1051.

Paper accepted but not yet published:

> Hess D. New therapies for asthma. Respir Care (year, in press).

Personal author book: (For any book, specific pages should be cited whenever possible.)

> DeRemee RA. Clinical profiles of diffuse interstitial pulmonary disease. New York: Futura; 1990. p. 76-85.

Corporate author book:

> American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

Chapter in book with editor(s):

> Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, editors. Pulmonary medicine. Philadelphia: JB Lippincott; 1977:26-42.

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Calendar of Events

AARC & AFFILIATES

March 31-April 1, 1999—*Newport, Rhode Island*

The RISRC presents its annual convention and exhibition at the DoubleTree Islander Hotel at Goat Island. Program topics include critical care, neonatal/pediatric, and ethical issues. The annual Respiratory Challenge competition will be held also.
Contact: Len Duffy at (401) 737-7010, or Wayne Foresti at (401) 769-8758.

March 31-April 1, 1999—*Salt Lake City, Utah*

The USRC is hosting its annual convention at the Salt Palace—Forecast for a New Millennium: Respiratory Therapists Shine Through. Topics will include patient assessment, protocols, ventilator waveform management, and alternative therapies.
Contact: Jim Keenan at (801) 588-3077, e-mail **pcjkeena@ihc.com.**

April 7-9, 1999—*Gulf Shores, Alabama*

The Alabama Society for Respiratory Care will be hosting their state educational meeting at the Gulf State Park Resort Hotel and Convention Center.
Contact: David Howard (205) 761-4573 or e-mail William.Howard@bhsala.com.

April 13-14, 1999—*King of Prussia, Pennsylvania*

The PSRC will host their 2nd Annual Eastern Regional Conference & Exhibition at the Holiday Inn. Guest speakers include Sam Giordano, MBA, RRT, and Richard Branson, BA, RRT.
Contact: Angie Herstine (609) 784-0340

April 21-23, 1999—*Cincinnati, Ohio*

The 26th Annual Region II Conference will be presented by the Indiana, Kentucky, and Ohio affiliates with an excellent mix of current topics and dynamic speakers.
Contact: Call (800) 691-3046, Mail Box I.or visit their web site at **http://www.bright,net/~dsibb/reg2rc.htm.**

April 23-25, 1999—*Kingsport, Tennessee*

The TSRC presents its annual convention and exhibition, The New Millennium: Somewhere Over the Rainbow, at the Meadowview Resort and Convention Center. Topics will include clinical, management, patient assessment, and student issues. 13 contact hours are available.
Contact: Colleen Schabacker (615) 384-1731

Other Meetings

March 14-17—*Orlando, Florida*

Noninvasive Ventilation, the seventh international conference of the American College of Chest Physicians, Independent Ventilator Users Network, and the AARC, is scheduled for the Caribe Royale Resort Suites. Topics include noninvasive ventilatory assistance in the home, ICU, ER, and long-term care sites; nutritional issues for ventilated patients; diagnosis and diagnostic methods; ethical issues; and telemonitoring in the home. Continuing education credits available.
Contact: (800) 343-2227

March 16-19, 1999—*Brussels, Belgium*

The 19th International Symposium on Intensive Care and Emergency Medicine will be head at the Congress Center in Brussels.
Contact: Ana Maria de Campos at 32.2 555 3215 or e-mail sympicu@resulb.ulb.ac.be.

March 24-27, 1999—*Big Sky, Montana*

The American Lung Association® of the Northern Rockies is hosting their 18th Annual Big Sky Pulmonary & Critical Care Medicine Conference at the Big Sky Ski Resort. The conference is a multidisciplinary review and update for all health professionals, and 15 hours of CME are available
Contact: ALA at (406) 442-6556 or e-mail **alamtwy@aol.com.**

March 24-27, 1999—*Denver, Colorado*

The *Journal of Emergency Medical Services* will host the 17th Annual EMS Today Conference and Exposition. Two clinical tracks will be offered for new and experienced providers, and special educational programs featuring the latest in EMS research will be featured. A rescue/special operations track will cover fire and rescue issues and important interface and safety aspects that exist between all emergency service agencies.
Contact: Call (800) 266-5367 or see the entire brochure online at **www.jems.com.**

March 25-28—*New Orleans, Louisiana*

The Southern Sleep Society will host its 21st annual meeting at the Hotel Monteleone.
Contact: Marietta Bellamy at (713) 781-0581 or e-mail **bellamy@bcm.tmc.edu.**

April 20-23—*Clearwater Beach, Florida*

All Children's Hospital of St. Petersburg, FL, will host their 1999 Neonatal/Pediatric Transport Conference at the Hilton Clearwater Beach Resort. The conference, titled Redefining State of the Art, includes a pre-conference lab and offers 23 CEUs.
Contact: Connie Spadaccino at (727) 892-4240 or (800) 456-4543, ext. 4240.

June 12-16, 1999—*International Society for Aerosols in Medicine*

12th International Congress at the Austria Center in Vienna, Austria. Topics include aerosol drug delivery, aerosol deposition and clearance, cellular and molecular interactions, environmental aerosols, standardization, aerosol diagnostics, and aerosol therapy.
Contact: Vienna Academy of Postgraduate Medical Education and Research. Alser Strasse 4, A-1090 Vienna, Austria. Phone (+43/1) 405 13 83-22, fax (+43/1) 405 13 83-23, e-mail medacad@via.at.

Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

Las Vegas

45TH INTERNATIONAL
RESPIRATORY CONGRESS
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Helpful Web Sites

American Association for Respiratory Care
http://www.aarc.org
- —Current job listings
- —American Respiratory Care Foundation fellowships, grants, & awards
- —Clinical Practice Guidelines

National Board for Respiratory Care
http://www.nbrc.org

RESPIRATORY CARE online
http://www.rcjournal.com
- —1997 Subject and Author Indexes
- —Contact the editorial staff

Asthma Management Model System
http://www.nhlbi.nih.gov

The National Board for Respiratory Care—1999 Examination Dates and Fees

Examination	Examination Date	Examination Fee
CRT Examination	July 10, 1999 Application Deadline: May 1, 1999	$120 (new applicant) 80 (reapplicant)
RRT Examination	December 4, 1999 Application Deadline: August 1, 1999	120 written only (new applicant) 80 written only (reapplicant)
CPFT Examination	June 5, 1999 Application Deadline. April 1, 1999	130 (new applicant) 100 (reapplicant)

For information about other services or fees, write to the National Board for Respiratory Care,
8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156,or e-mail: nbrc-info@nbrc.org

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In this issue
1999 Call
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Successful CPT Coding Teleconference April 13, 1999

A 90-minute audio teleconference will give you the chance to speak directly with a CPT coding expert to learn new coding strategies and how to minimize costly mistakes. The program has been approved for one hour of continuing education credit by the AARC and by the Texas Nursing Association. The speaker will be Kevin Shrake, MA, FACHE, Administrator of Cardiovascular and Critical Care Services at St John's Mercy Medical Center in St Louis MO. The subjects covered are: Background of CPT Coding; Resources Needed to Evaluate Coding Systems; Tips on Interpreting the CPT Code Manual; Selecting the Right CPT Code; Matching Revenue Codes; Split Billing; Strategies for Successful Coding; Common Sources of Billing/Coding Errors. Call the AARC at (972) 243-2272 for more informaton; call KRM Information Services at (800) 775-7654 to register.

Patient Assessment Course for Respiratory Therapists

Due to overwhelming demand, the patient assessment course for respiratory therapists will be offered twice this year. Space is at a premium and preregistration is required. Successful completion of the course will earn participants 16 hours of CRCE credit and a certificate of course completion. Each attendee will be given a pocket guide to physical assessment, to help them on the job. Following the last class, participants will take a 100-item test developed by the NBRC. Tests will be graded on-site for those wishing to obtain their scores immediately. Locations and Dates: Philadelphia: April 30-May 2; Phoenix: July 18-20 (immediately following Summer Forum). For more information and to register, visit the AARC web site at www.aarc.org.

AARC, Affiliates Set Conference Schedules

The AARC and many of the affiliates have set their schedules for 1999 conferences and seminars. Foremost among AARC's offerings are its Summer Forum (July 16-18) and Annual International Respiratory Congress (Dec. 13-16). Check out the AARC's website at www.aarc.org for all meeting registration materials and a list of affiliate conferences.

Videoconference Program Set; Nursing CEUs Offered

A series of eight videoconferences are scheduled for 1999 through the AARC Professor's Rounds series, which are now approved for nursing CEUs as well as CRCE credit. Topics are: respiratory assessment, asthma management, ventilator management, disease management, pediatric emergencies, COPD, PEEP, and respiratory pharmacology.

CRCE Online Debuts

Now you can earn continuing education on the Internet from the AARC through its new CRCE Online website. After you pay for the number of continuing education units you wish to attempt (by submitting your credit card number on a secure server site), you are given access to the list of courses. Read the material, take the test, and then print out a certificate showing you passed. Your participation will also be noted on your CRCE record with the AARC. Log on to the AARC's website at www.aarc.org and look for CRCE Online.

Authors in This Issue

Aranda, Margaret . . . 156
Bacha, Emile A . . . 205
Bateman, Scot T . . . 177
Baum, Victor C . . . 196
Betit, Peter . . . 177
Boyle, Kathy . . . 225
Channick, Richard N . . . 212
Gerlach, Herwig . . . 184
Gerlach, Marlene . . . 184
Goss, Christopher H . . . 222
Henig, Noreen Roth . . . 223
Hess, Dean R . . . 155
Hurford, William E . . . 155
Keh, Didier . . . 184
Lowson, Stuart M . . . 196
Pearl, Ronald G . . . 156
Rich, George F . . . 196
Roberts, Jesse D Jr . . . 169
Stanford, Derek . . . 224
Thompson, John . . . 177
Yung, Gordon L . . . 212

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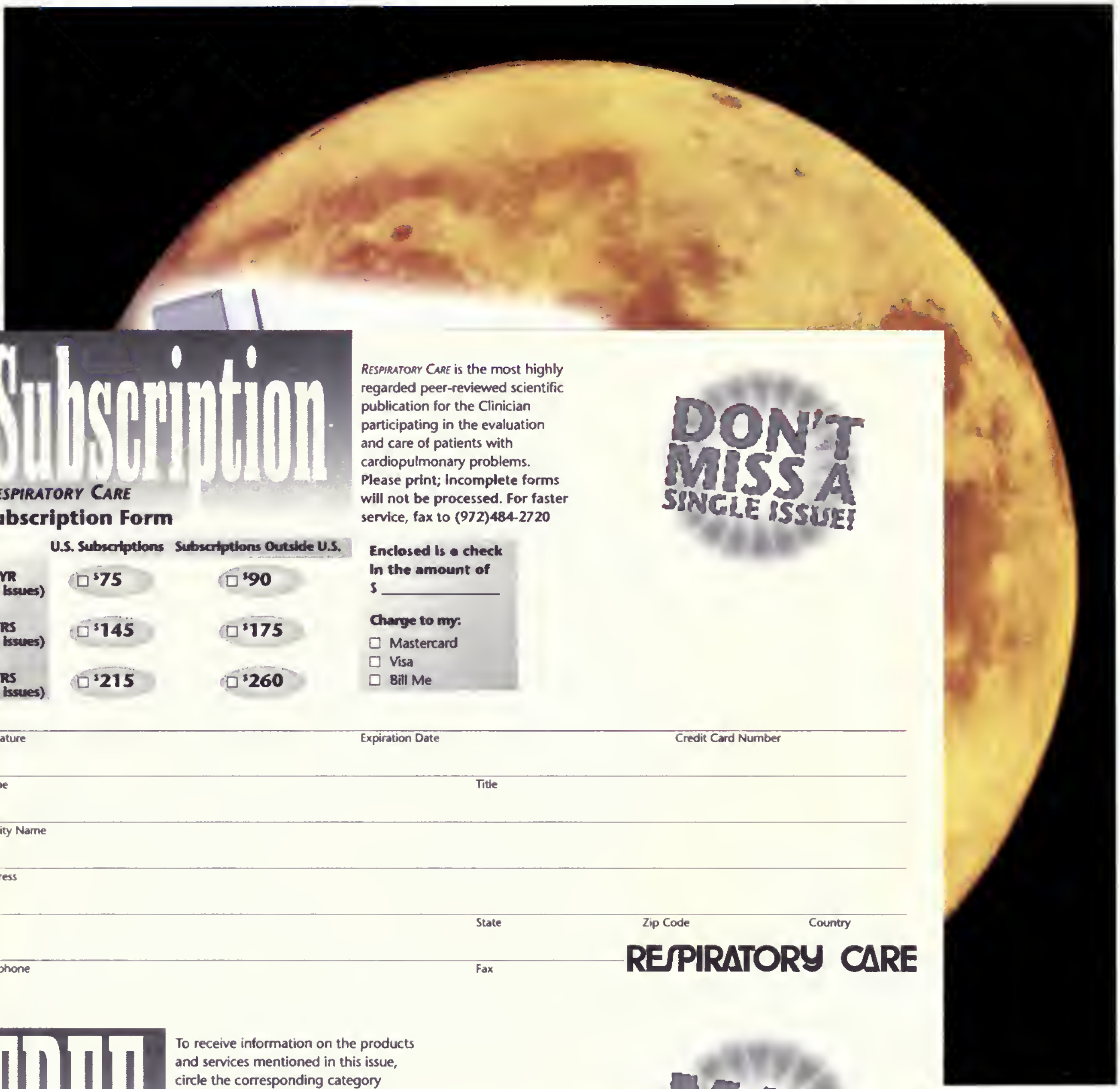

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137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154
155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172
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February 1999 Expires 5/15/99

I TYPE OF INSTITUTION OR PRACTICE
- 1 ☐ Hospital
- 2 ☐ Skilled Nursing Facility
- 3 ☐ Subacute Care Facility
- 4 ☐ Home Care Practice
- 5 ☐ School
- 6 ☐ Distributor

II DEPARTMENT
- A ☐ Respiratory Care
- B ☐ Cardiopulmonary
- C ☐ Subacute Care
- D ☐ Home Care

III SPECIALTY
- 1 ☐ Clinician
- 2 ☐ Perinatal/ Pediatrics
- 3 ☐ Critical Care
- 4 ☐ Research
- 5 ☐ Subacute Care
- 6 ☐ Diagnostics/ Pulmonary Function
- 7 ☐ Management
- 8 ☐ Home Care
- 9 ☐ Rehabilitation
- 10 ☐ Education

IV POSITION
- A ☐ Department Head
- B ☐ Chief Therapist
- C ☐ Supervisor
- D ☐ Staff Therapist/ Technician
- E ☐ Medical Director
- F ☐ Educator/Instructor
- G ☐ Sales
- H ☐ Other (please specify) ____

V ARE YOU AN AARC MEMBER?
1 ☐ Yes 2 ☐ No

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17 33

Authors in This Issue

Aranda, Margaret 156
Bacha, Emile A 205
Bateman, Scot T 177
Baum, Victor C 196
Betit, Peter 177
Boyle, Kathy 225
Channick, Richard N 212
Gerlach, Herwig 184
Gerlach, Marlene 184
Goss, Christopher H 222
Henig, Noreen Roth 223
Hess, Dean R. 155
Hurford, William E 155
Keh, Didier 184
Lowson, Stuart M 196
Pearl, Ronald G 156
Rich, George F 196
Roberts, Jesse D Jr 169
Stanford, Derek 224
Thompson, John 177
Yung, Gordon L 212

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Mahlmeister MJ, Fink JB, Hoffman GL, Fifer LF, "Positive-expiratory-pressure mask therapy: Theoretical and Practical Considerations and a Review of the Literature", *Respiratory Care*, 1991; 36:1218-1230.

[2] Ibid.

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